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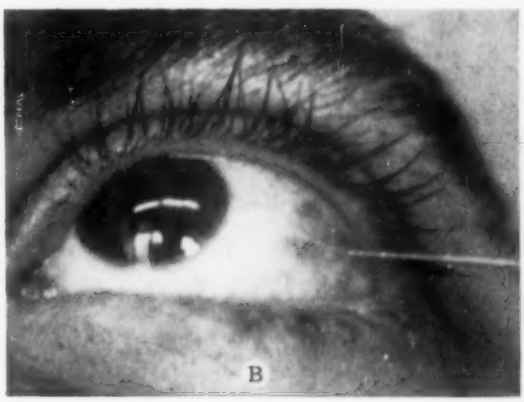

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It was decided to try cosmetic contact lenses on the boy. The procedure of fitting these lenses is as follows. A mold is made of both eyes and from these molds regular contact lenses are made, incorporating any corrections that are necessary. These lenses are worn and adjusted until the patient is comfortable. Due to the lack of pupil "stops" the vision may not be all that is desired, but the mechanical wearability must be satisfactory. From these lenses opaque lenses are made, and on each lens the iris is painted by hand, leaving the pupillary areas clear. The optics necessary to satisfy the prescriptions are then ground on the pupillary areas and the lenses are ready for use.

With the proper light control as provided for by the painted iris, the vision in the case we are describing was very much improved. The improvement in appearance was remarkable. To any but a trained optical person, the boy's eyes were normal in every way.

Cosmetic contact lenses are also very often indicated where disfiguring burns or other accidents have marred the appearance of the patient. The same procedure is followed. If no distance correction is needed, the lenses can be ground without correction.

An aside here may be interesting. The first known contact lenses were used during the French revolution. They were not worn to improve vision but to change the color of the wearer's eyes and in so doing act as a disguise.

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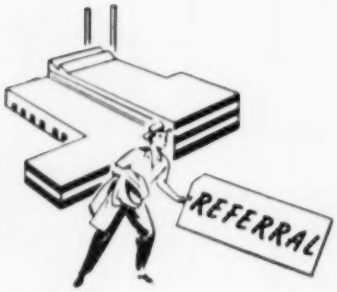

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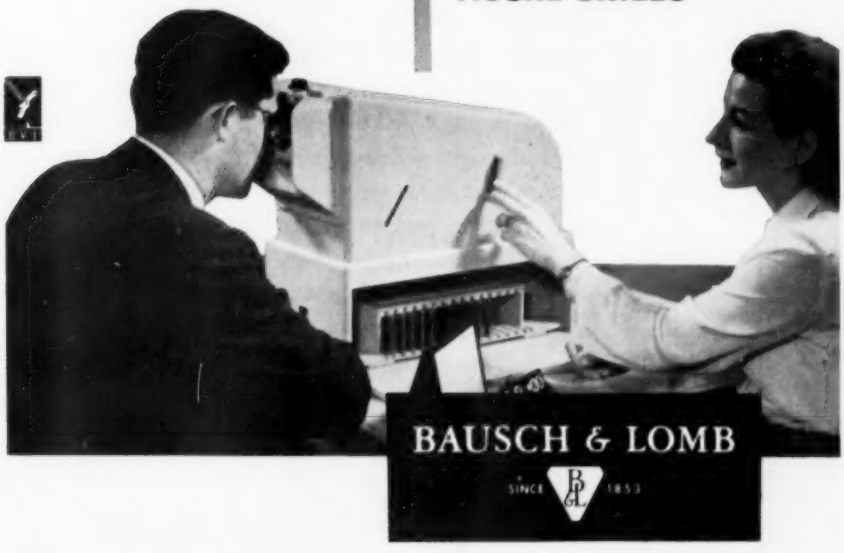

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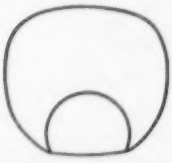

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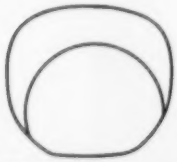

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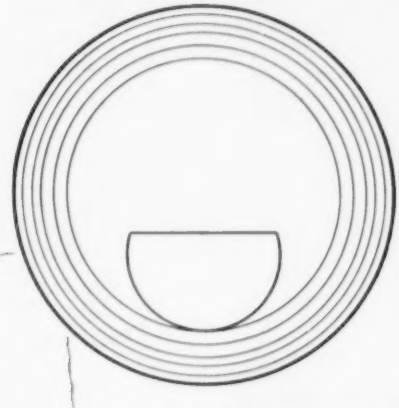

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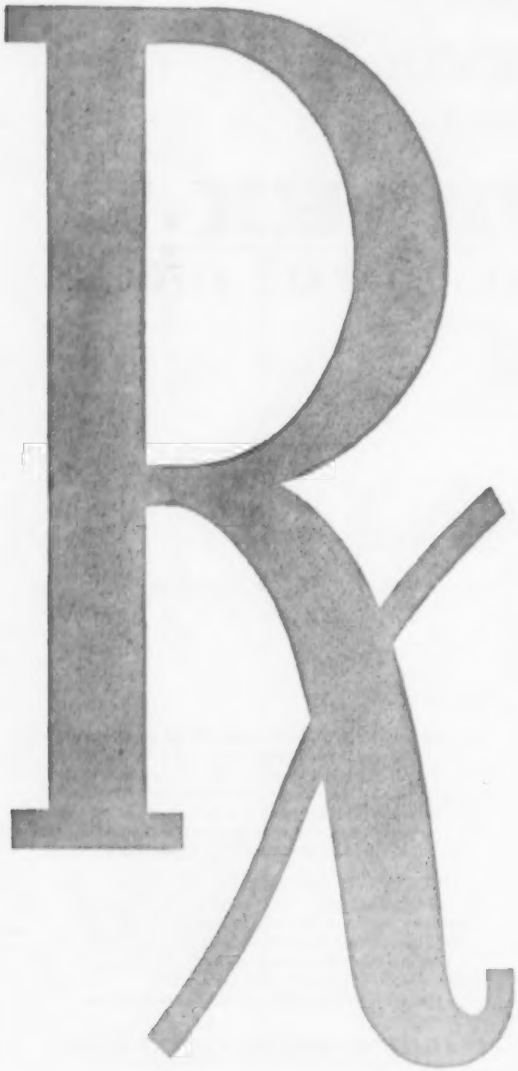

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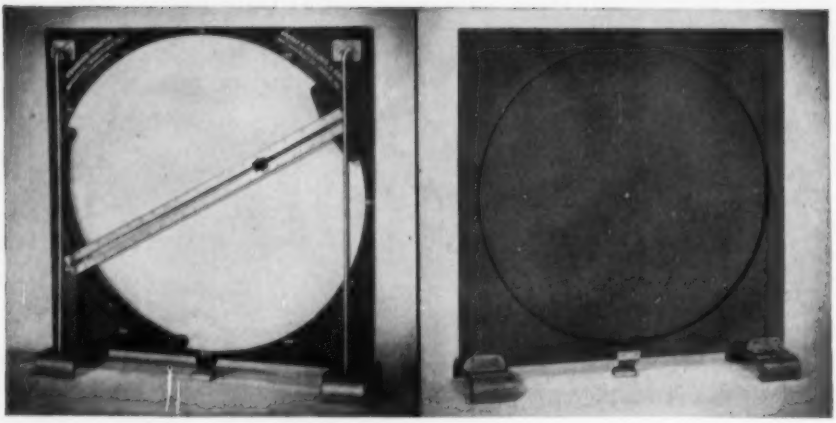

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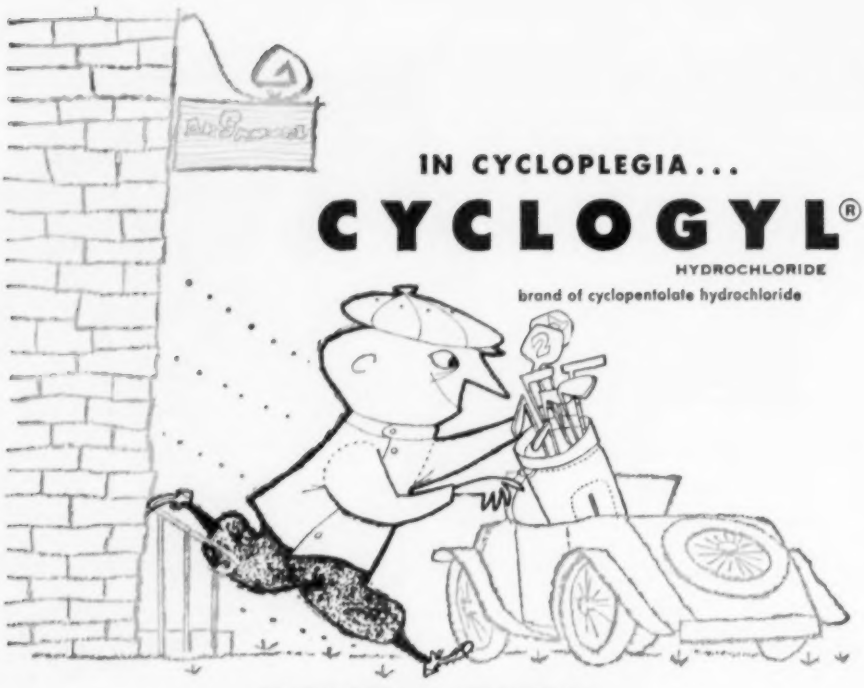

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1. Gordon, D. M., and Ehrenberg, M. H.: Am. J. Ophth. 38:831 (Dec.) 1954.

"the chief handicap of maximum cycloplegia, namely its incapacitating effect, is minimized . . ."
Getter, B. C.: A.M.A. Arch. Ophth. 51:467 (Apr.) 1954.

Cyclogyl, "by virtue of its brevity, rapidity of action, and consistent depth of cycloplegia, will be [a drug of choice] for routine refraction . . ." *Ehrlich, L. H.: New York J. Med. 53:3015 (Dec. 15) 1953.*

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The Impact of Boxing upon the Visual Apparatus

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Boxing devotees are no exception to the rule that men can always evolve a set of reasons to justify their favorite pleasure; and even if their arguments be exposed as fallacies, those who love a fight will readily produce alternative pleas to support their craze. Before we look at some of the conventional arguments for boxing, let it be emphasized that many of us possess firsthand evidence against Haislet's contention that the sport is not dangerous. "The injuries that do occur," he says, "are *minor and are not serious*" (my italics). According to him, there are *"no permanent scars or injuries"* (my italics again). Anyone who can believe those statements in defiance of the facts has no right to despise an ostrich for burying his head in the sand. The literature contains many records of eyes wrecked by boxing, and we must also remember that the eyes and their adnexa, though necessary for vision, are nevertheless incapable of appreciating images or making visual judgments. The act of seeing is mediated by almost inconceivably complicated cells and fibers extending through that organ which every boxer's opponent strives to knock out of action.

Battles with fists are in many men's minds hallowed by their youthful recollections. The thought of a bully being thrashed by some chivalrous rescuer often sets a boy's heart aglow, and probably at some stage in his development he will have devoured stories of the ring. For more than half a century juvenile magazines have catered to this demand on a large scale, and among the popular boxing novelists of this century were Conan Doyle, Jack London, and Jeffrey Farnol.

One of the earliest descriptions of a cad being routed can be found in that enchanting epic "The Odyssey," composed for recital by bards nearly 3000 years ago. Odysseus, returning to his own palace in the guise of a beggar, was rudely threatened by Arnaeus (nicknamed Irus). When Odysseus answered him in manly terms, Arnaeus became even more offensive, much to the delight of Penelope's suitors, who scented a battle. They decided that the two beggars must settle the issue with fists, and it was agreed that the victor's prize should be one of the stuffed goat paunches roasting by the fire. Odysseus was in two minds whether, as Lawrence of Arabia puts it in his translation, "to smite the other so starkly that life would leave him where he fell, or to tap him gently and just stretch him out. On the whole the gentle way seemed right, to save himself from too close notice by the Achaeans. So when they put up their hands and Irus hit at his right shoulder, Odysseus only hooked him to the neck under the ear and crushed

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the bones inward, so that blood gushed purple from his lips and with a shriek he fell in the dust, biting the ground and drumming with his feet. The suitor lords flung up their hands and died of laughing; but Odysseus took him by the leg and dragged him through the entrance, across the yard and to the outergate, where he propped him with his back against the precinct-fence and his beggar's crutch between his hands, remarking bitterly, 'Sit there and play bogy to the dogs and pigs: but unless you want a worse beating never again set up your silly self as beggarking.'" Odysseus' punch was surely as devastating as anything recorded of Rocky Marciano.

Other vivid descriptions of fisticuffs will be found in the work of Hazlitt, the essayist, and of George Borrow, who was himself a keen performer with the gloves; and it seems clear that champion fighters throughout the 19th century were as high in public favor as they are today, although the methods of attaining publicity were different. Gentleman Jackson, who remained in the forefront of boxing for years, was a friend of Lord Byron, and all the bucks of the sporting world came to his sparring rooms in Bond Street. Another great figure was Bendigo, of Nottingham, a triplet and the youngest of 21 children. From the age of 21, when he became a prizefighter, until he retired in his 40th year, he never lost a fight, although nearly all his opponents were taller and heavier than he was. He sometimes maddened them by his laughter and antics, and would even turn a somersault after some particularly telling punch. More than one of his fights went on for over two hours in blazing sunshine, and twice he won in the 93d round. Bendigo's fame spread so far that a town was named after him in Australia. On retiring from the ring, alas, he took to drinking and political brawls, and often found himself in prison.

During his last spell of imprisonment Bendigo was converted to religion. He became an enthusiastic preacher, and sat on the platform with another Nottingham man, General Booth, of the Salvation Army. Extracts from his talk at the London Cabman's Mission Hall bear the stamp of a Buchmanite testimony. For instance, he said: "It's two years since Jesus came to me, and had a bout with me, and I can tell you he licked me in the first round. He got me down on my knees in the first round and there I found grace." At one revivalist meeting in a crowed hall, some roughs kept on jeering, and Conan Doyle has memorably recorded the shambles that ensued.

He vaulted from the pulpit like a tiger from a den,
They say it was a lovely sight to see him floor his men;
Right and left, and left and right, straight and true and hard,
Till the Ebenezer Chapel looked more like a knacker's yard.
Platt was standin' on his back and lookin' at his toes,
Solly Jones of Perry Bar was feelin' for his nose,
Connor of the Bull Ring had all that he could do
Rakin' for his ivories that lay about the pew.

Many people wonder how the old pugilists were able to endure their mutual battering for 90 rounds and more without the boon of gloves. The answer is simple. Gloves are a safeguard for the striker, not the victim. The old champion's stance, as exemplified by Richard Humphreys, shows that their contests were essentially slugging matches. If they had known how to put all their weight into a properly timed blow on the jaw, their metacarpals would soon have been reduced to pulp. One gloved punch by a modern expert would send them spinning if it were to hit the proper place half an inch to either side of the mandibular symphysis, from which area a shock is conveyed to the otocyst. Such a blow, as Sherrington [10] (1947) remarked, "reduces in a moment a vigorous athlete to an unstrung bulk of flesh whose weight alone determines its attitude, if indeed a reactionless man can be described as possessing attitude at all." At Jersey City, in 1921, Carpentier, whose right-hand punch had floored all his European rivals, nearly knocked out Dempsey in the second round, but perhaps the blow fell a fraction wide of the vital spot, or perhaps Dempsey was saved by those extra layers of jaw muscle which he had assiduously cultivated by the chewing of resin gum. Be that as it may, the impact

broke Carpentier's right thumb in spite of the gloves, and Dempsey dispatched him two rounds later.

Before we part from the warriors of bygone days, let us salute the most picturesque of them all, John L. Sullivan, the Strong Boy of Boston, a formidable champion who once pounded Jake Kilrain for 75 rounds. Theodore Dreiser vividly describes Sullivan in retirement, red-faced, overdressed, and bejeweled, lolling in the midst of champagne buckets and cigar boxes, surrounded by the most degraded of local sports and politicians. But there was something about Sullivan, even in the days of his decline, so that Dreiser had to end by saying, "I adored him." Then, again, a writer who quoted some correspondent's description of Sullivan as "a son of a bitch of the first water, if he ever drank any," went on to point out that Sullivan, nevertheless, was a god and that he was adored.

THE VINDICATION OF BOXING

When people offer reasons in justification of boxing, they usually assume, or pretend to assume, that the risk of serious mental and physical damage is negligible. Some of them carry wishful thinking a stage further and persuade themselves that the fair-haired stripling with right on his side will usually beat the bulky ruffian even if the latter resorts to foul methods. Many people also proclaim the usefulness of boxing knowledge as a means of defense against blackguards and slubberdegullions, but, unfortunately, the efficient thug does not stand facing his intended victim in a good light, waiting to be hit on the side of the chin. If his fists come into the picture at all, they will be buttressed with knuckle dusters; but probably he will use a knife, a revolver, or at least a spanner. Moreover, jujitsu experts and trained wrestlers without adventitious weapons can soon put a boxer out of action. Perhaps the most curious argument ever advanced in favor of fisticuffs is that of George Borrow. In his gypsy book "The Romany Rye" he calls it "a fine, manly English art, and a great defense against Popery," but of course he lived in the days when almost every dispute was assessed in relation to theology.

Extremists have maintained that a certain amount of ocular damage does not matter, because defective sight is not incompatible with prowess in the ring. Did not Slugger White's artificial eye pop out on the floor while he was being medically examined before a fight in San Francisco? And what about the Boston Tar Baby, Sam Langford? Vision in his right eye was far below normal when the other eye went blind in 1917, but he went on fighting until one day in 1924, when he was observed wandering vaguely about the ring looking for the opponent he had knocked down. It is astonishing how much sporting achievement stands to the credit of partially sighted, and even of blind, people. There was Charles Boswell, the blind golfer, who played 18 holes in 82 strokes at Birmingham, Ala.; and Don Morgan, who stroked one of the Cornell crews after losing the sight of both eyes. Wrestling championships have been won by blind competitors, and recently Sid Silcock, a totally blind ex-serviceman, became bowls champion of the Terralba Club near Newcastle, in Australia. There is no doubt that some people redouble their efforts under the spur of a disability. Ben Hogan had the guts to win the American Open Golf Championship in the year following an accident, in which he sustained a crushed shoulder, leg fractures, crushed pelvis, and pulmonary embolus. Walter Davis, of Texas, who high-jumped 6 ft. 11½ in., caught poliomyelitis in childhood. So did Tenley Albright, but she went on to win the world figure-skating championship. Let us by all means pay tribute to those who have the courage to overcome physical handicaps, but still it remains true that the scales are heavily weighted against any man embarking upon a fight without the faculty of clear vision.

Humor is a useful brush for whitewashing the ring. Boxing fans gleefully fasten upon items of damage arising in the course of more sedate pastimes. Suppose that a boxer is flipped on the eye by a Ping-pong ball. "Oh yes," they will say, wagging their heads

in mock solemnity, "he'd much better have stuck to boxing. It's so much safer." Then they collect amusing examples of players being accidentally hit on the head by a croquet mallet or knocked unconscious on the tennis court. Football supplies them with more solid ammunition, because there is undoubtedly a long list of injuries produced by this game, even if we exclude damage arising from foul play. In this connection, however, we should remember three things. First, the number of footballers vastly exceeds the combined total of amateur and professional boxers. Secondly, the rules of football forbid any deliberate infliction of injury, whereas the prime object of boxing is to knock your opponent unconscious. Thirdly, the damage sustained at football, even if it be permanent, is far more likely to be located in the limbs than in the head. From time to time footballers are concussed, and very rarely there has been a death; but this game creates no genuine counterpart to the slap-happy veterans of the ring.

Clearly there is some truth in the contention that boxing promotes endurance, quickfootedness, and muscular development. On the other hand, many other forms of sport offer the same or greater benefits without the disadvantages inherent in pugilism. One objectionable feature of boxing is that it tends to develop the upper half of the body out of proportion to the lower. Furthermore, the intensive bouts of exercise, together with drastic, rapid alterations in weight necessitated by an impending fight, often drive boxers to fling up the sponge and abandon asceticism as soon as they go out to grass. Although there are several noteworthy examples to the contrary, it is evident that retired boxers are only too liable to sag.

We have already seen that the art of boxing does not qualify a man to protect others or himself from jujitsu exponents or efficient thugs. Nor should boxing be countenanced as a form of exercise if in fact it entails unreasonable risks. To what extent can the hazards be lessened by medical control? Romino [9] (1949) suggested equality of matching, medical records of each fight, and prohibition of boxers from fights within three months of their having been knocked out. Albaugh [1] (1952) points out that the State of California will not grant a boxing license without general and ocular examination by a physician; and the licensee must afterward submit to reexamination annually, as well as on other necessary occasions. Licenses are no longer granted to one-eyed boxers, or to those suffering from defective sight and ocular disease. Moreover, the referees have instructions to stop a fight as soon as it is manifest that one of the combatants is hopelessly outclassed. Similarly, the British Board of Control has evolved a set of precautionary rules and instructions, as set forth by Graham [3] (1955). Such measures have no doubt mitigated the crudities of the old system, or lack of system; but there is no real safeguard against a series of scientifically planned blows alighting time after time upon the most vulnerable regions of the head and face. Incidentally, we shall see that fists are not the only instruments of destruction in a boxing contest.

RANGE OF BOXING INJURIES

Head collisions between two boxers sometimes decide the issue of a fight, and there is evidence to show that this method of wounding an opponent may be deliberate. Referees cannot always be sure, during a whirlwind of close in-fighting, whether any particular collision was the effect of a butt. One consequence is that an insecure scar upon the eyebrow may be reopened, and so vision is obscured by a stream of blood flowing down the victim's face. Sometimes the results are more serious, because one of the combatants may be bumped on the thinnest part of his cranium while the other receives the impact on relatively dense bone.

Another menace to a boxer's skull is the floor. Kaplan and Browder [5] (1954) have recorded the results of postmortem examinations upon five boxers killed in the New York district, and in each instance they ascribed death to contusion and laceration of the frontotemporal region of the brain from a fall on the occiput. With the object of

minimizing such risks, boxing authorities have put rubber and other forms of resilient material under the floor canvas, and a special type of flooring designed by Cornell University is being tried elsewhere. It seems improbable, however, that fatalities will be altogether prevented, because, when punches are rained in quick succession, more than one of them may strike an already unconscious man, who thereupon pitches heavily onto the floor.

Derangement of the visual apparatus from boxing may conveniently be divided into (1) ocular damage; (2) injuries to neighboring structures, including the ocular adnexa, and (3) lesions of the visual pathways and other parts of the brain.

1. Ocular Damage

One important asset to a boxer is a pair of well-formed orbital margins, but his eyes are nevertheless liable to be damaged by blows falling tangentially upon the cornea from a downward and outward direction, where the orbital cavity is at its shallowest. Moreover, the thumb of a boxing glove can easily impinge upon the eyes even if they be deeply set; hence boxing is particularly dangerous for myopes, because their eyes are not only more prominent but more vulnerable than those of the average emmetrope.

(*a*) *Lesions of the Outer Eye.*—Conjunctival hemorrhages are not in themselves of much importance, but they may, of course, be accompanied by damage to other structures. Any or all of the corneal layers may be injured. Small abrasions may heal uneventfully, but larger ones are liable to infection; and the resulting ulcers will sometimes leave dense opacity in their train. Edema and striate opacity of the substantia propria have been repeatedly observed, and Descemet's membrane may be folded or ruptured. Scleral rupture is another serious possibility to be borne in mind, because it can at first be masked by conjunctival hemorrhage, and will commonly be associated with damage to the inner eye.

(*b*) *Lesions of the Inner Eye.*—These occur in bewildering variety. Hyphema often arises from iris hemorrhage and will at first preclude detailed inspection of the fundus. The iris itself may display single or multiple ruptures of the pupillary margin, with or without implication of the sphincter muscle; or its ciliary margin may be partly torn across to produce an iridodialysis. Occasionally the whole peripheral attachment of the iris gives way, and the retracted ball of uveal tissue is later seen lying free in the anterior chamber. Interference with the ciliary body is presumably the explanation for that persistent hypotony which has been detected in some boxers, and sometimes an insidious iridocyclitis supervenes. The worst cases advance relentlessly to a state of phthisis bulbi. Occasionally a lesion of the ciliary body is limited to its muscle; whence follows paralysis of accommodation. The lens may be subluxated or totally dislocated, and cataract is not uncommon. In this connection, it must be remembered that the full effect of lens concussion may be delayed for months or years. Thus, eyes apparently undamaged may in fact have sustained stresses which will betray themselves after a lag. Cataract may also emerge as a complication of cyclitis in an eye damaged by boxing.

Hemorrhage into the vitreous may be derived from the anterior or the posterior segment of the globe or from both. In all except very severe cases, absorption tends at first to be complete, but repeated hemorrhages encourage the deposition of those fibrous strands which perhaps herald retinitis proliferans. Retinal detachment is one of the most dreaded consequences of boxing, and a number of bilateral cases are recorded in the literature. Here it must be emphasized that the chances of permanent reposition by surgical treatment are much less than they are in other types of juvenile detachment. Among those who have testified to this effect is Albaugh.[1] Operation was considered feasible in only 5 out of his series of 29 retinal detachments due to boxing, and even among these 5, relatively favorable, cases, only one retina was successfully reattached. Cystic and pigmentary changes at the macula are another tragic outcome of blows upon the

eyes, and retinal hemorrhages are commoner than many people realize.

Choroidal hemorrhages are even more destructive, and almost certainly originate those irregularly shaped, mottled, raised areas of degeneration which are so ophthalmoscopically conspicuous in the seasoned pugilist. Whenever we see a bruiser with a pair of cauliflower ears, let us be on the lookout for cauliflower choroids. These multiple fundus lesions account for many a boxer's defective visual acuity. Then, again, a choroidal rupture may involve the macula. Optic atrophy is another possible fundus finding. Avulsion of the optic nerve can produce complete atrophy, and so can hemorrhage into the nerve sheaths. Partial consecutive atrophy is a sequel of repeated traumatic hemorrhage, especially from the choroid.

Recurrent congestive glaucoma is another potential danger for a man exposed to repeated blows upon the eyes, and this condition may produce a blind, painful eye; but it is abundantly clear that, for every troublesome eye which has to be removed, several remain as nonfunctioning, though painless, vestiges, and in many others vision is permanently curtailed.

2. Injuries to Neighboring Structures, Including the Ocular Adnexa

Diffuse thickening of the bone along the orbital margins is not uncommonly evident in ring veterans. Localized hyperostoses have also been found encroaching upon the orbital cavity. Any of the bones that form the orbit may be fractured, especially the ethmoid, maxilla, malar, and lacrimal bones. Orbital emphysema is apt to arise when the accessory air cells, especially those of the ethmoid, are involved in a fracture; and obstruction of the nasolacrimal duct is one of the complications of a broken nose. The lacrimal gland itself may suffer damage, and another possible source of deranged lacrimal function is injury to a canaliculus. Stallard[13] (1951) reported severance of the left superior and inferior lacrimal canaliculi from a punch landed in amateur army boxing. Conjunctivodacryocystostomy had to be performed. Bruising of the eyelids constitutes an ordinary "black eye," and is not usually serious, but sometimes ptosis occurs from damage to the levator palpebrae superioris.

Any of the extraocular muscles may be implicated, but the superior and inferior obliques are the most directly vulnerable because they so nearly approach the anterior margin of the orbit. Even in the absence of direct muscular injury, e. g., laceration, the action of the recti muscles, as well as that of the obliques, may be impeded by connective tissue developing after repeated hemorrhage into the orbit. It will be remembered that most of the interstices between the orbital structures are filled with fat, a tissue slow to absorb effused fluid; and absorption tends to be progressively slowed if these orbital hemorrhages keep on recurring. Limitation of movement in one or more directions, and sometimes in all directions, has accordingly been registered in many boxers. Operations undertaken with the object of improving ocular motility in such cases are apt to be frustrated by adhesions which obscure the anatomical landmarks normally encountered in this cavity.

Divergent squint is often manifest when one eye has been rendered blind or grossly defective; and high degrees of exophoria have been recorded even among those with equal vision in the two eyes. In some countries boxers suffering from diplopia are banned from official matches, but we have to remember that the ocular muscle balance can be seriously deranged even in a patient not complaining of double vision. It has been playfully suggested that diplopia may stimulate a boxer to punch harder in the hope of knocking out two opponents with one blow, but Whiting's[14] (1951) patient, Bill Softly, was assuredly handicapped by reduplication of his images. "Yes," he said, "I see two chaps in the ring and I hit the one that isn't there and the one that is there hits me."

3. Lesions of the Visual Pathway and Other Parts of the Brain

When physiologists first succeeded in mapping out the different regions of the brain,

it was confidently supposed that sooner or later every part would be accorded a precise function, and that all localized lesions would elicit a calculable defect. These hopes have been tempered by modern knowledge. Experimental and clinical studies have shown that substantial portions of the cerebral hemispheres may be lost without any obvious loss of efficiency. Thus, people who have sustained a severe head injury, including skull fracture and laceration of the brain, are sometimes able to resume their family life and their jobs as though the accident had never occurred. It seems clear that certain parts of the brain are adaptable. That is to say, they can take over the function of a damaged area. This flexible arrangement is not, of course, applicable to all regions, but it does mean that most human beings possess reserve cerebral tissue in large measure, enabling them to withstand limited injury. Nevertheless, they are more vulnerable after such damage to the brain. Symonds [12] (1941) emphasized that a patient who has made an apparently complete recovery may afterward react with disproportionate intensity to a much slighter head injury, because he has already, so to speak, taken up his slack, or drawn on his reserves.

Symonds' clear exposition of *latent* impairment of the brain is amply illustrated by many a boxer's career. There are many gradations of traumatic encephalopathy before a man reaches the state of complete punch-drunkenness, and it has now been shown that hemorrhage and reactive fibrosis of the brain are evoked by relatively slight blows upon the head. Taylor [13] (1953) has written a vivid account of a 26-year-old miner whose personality showed appalling changes within a few years of his entering the professional ring. He became egocentric, garrulous, boastful, and paranoid, and entered a mental hospital after threatening his wife with a carving knife. After six months' sedation and rehabilitation he was able to leave hospital but was fit only for unskilled labor. He had residual amnesia concerning weeks at the time of his last two fights, and the electroencephalogram showed reduced activity on all leads.

Generalization on the score of an isolated case would be wrong, but in fact the literature contains numerous accounts similar to that of Taylor. Winterstein [15] (1937) made a clinical study of professional boxers at Guy's Hospital and found many instances of slurred speech, vacant gaze, disordered equilibrium, poor memory, low intelligence, paranoia, and garrulous euphoria. Similar hallmarks of traumatic encephalopathy are mentioned by Parker [8] (1934), and Maitland [7] (1928) estimated that nearly half of the regular professional boxers displayed a brain defect sooner or later. One of the most comprehensive studies was made by Carroll [2] (1936), who not only examined numerous boxers, but also frequented their training quarters and talked with sporting journalists. He paints an unforgettable picture of the typical sturdy young fighter who goes in for gymnasium training interspersed with perhaps 30 to 40 short amateur contests. Granted a modicum of success, he turns professional and will probably fight several dozen times during the next few years. Unless he can develop that degree of skill and nimbleness which only a small minority can achieve, he will then begin to "soften up." One sign of general neuronic deterioration is reduced tolerance to head blows. His defense becomes less effective, and his punches are less well timed. Boxing journalists are apt to write with pained surprise about the poor showing made in some particular fight by a hitherto stout-hearted pugilist. If only they would learn a few elementary facts about the anatomy and physiology of the brain, the explanation would readily emerge. Better still, let them attend a few postmortem examinations upon those who succumb to boxing, so that they can see what havoc may be wrought upon the lobes of a repeatedly hammered brain.

Gene Tunney got out before it was too late. In the course of a training bout he was punched into a mental twilight for three days, and that incident made him determine to

leave the ring. Carroll [2] quotes him as saying: "I wanted to leave the game that had threatened my sanity before I met with an accident in a real fight with 6-ounce gloves that would permanently hurt my brain." These words were uttered not by a weakling or a coward. They were the words of a man who twice defeated the redoubtable Dempsey and stood up round after round to fearful punishment from Harry Greb. Tunney's decision should be more widely proclaimed, because even the most fanatical of boxing zealots will find his words hard to explain away.

Although the anatomy of the visual pathway has been established by countless histological demonstrations and verified by electroencephalography, we should always bear in mind that many other parts of the brain are concerned with visual interpretation and spatial judgments. Therefore a boxer's power to use his eyes effectively can run to seed without there being any demonstrable ocular lesion or any interruption of the visual fibers. We know that repeated blows on the head make for fibrous strangulation of nerve cells and dendrites, but there are several other important ways in which the brain may be jeopardized. In the first place, the pons and medulla may be nipped over the tentorium when an extra punch bends the cervical spine of a semiconscious boxer with relaxed muscles. Secondly, deposits of scar tissue can interfere with the circulation of cerebrospinal fluid, as well as destroy neurones. Thirdly, there is a risk of subdural or subarachnoid hemorrhage.

MAIN CONCLUSIONS ABOUT BOXING, AMATEUR AND PROFESSIONAL

Many people suppose that the major hazards of boxing are confined to professionals. They admit that the careerist boxer is in grave danger, especially if he continues to fight after the age of 30, but they maintain that amateur boxing is practically safe. They should consult the writings of Jokl [4] (1941), who has been an authority on this subject for many years. Macular lesions, retinal detachments, and other serious ocular lesions have been noted by Jokl and many others in early-teen-age boys. Young adults have died of middle meningeal hemorrhage after relatively slight blows on the head, and others have suffered lasting brain damage.

In recording the verdict of death by misadventure upon a French boxer who died two days after being defeated in a flyweight championship, a London coroner (1952) said: "I am sure every precaution was, and is, taken in these fights." A postmortem examination had shown that a small vein between the brain and the skull was ruptured, but it is likely that routine medical testing before the fight could have revealed his liability to this fatal accident? The coroner's words were no doubt justified as a means of consoling the near relations, but from other standpoints they could only be self-deception, or else a piece of official "soft soap."

If all boxers before every contest were submitted to thorough clinical examination, together with elaborate laboratory, radiographic, ophthalmoscopic, and other special investigations, and if all these precautionary tests were to yield negative results, the boxer might still be damaged for life or fatally injured in the first round. Admittedly, medical supervision can pick out various unequivocal defects, and exclude from championship fighting the manifest cripples and morons, but it cannot alter the anatomy of the human skull or lessen the delicacy of those organs which subserve our highest faculties. All medically qualified people have had the opportunity to dissect the head and neck. These are not the only targets for disabling blows, but we know that they are the most important, because they contain the seat of intelligence, together with a most fragile set of sense organs, a sequence of delicate nerves, and a number of other structures nourished by richly anastomosing blood vessels. The very thought of setting out to smash all this artistry with fists is sacrilege, not sport, and it behooves us to speak out against such barbarism.

"It is probable," says Carroll [2] (1936) "that no head blow is taken with impunity, and that each knock-out causes definite and irreparable damage. If such trauma is repeated for a long enough period it is inevitable that nerve-cell insufficiency will develop ultimately, and the victim will become punch-drunk." Listen also to the testimony of Laurie [6] (1955), who has attended more than 2,000 bouts as medical officer to a prominent amateur boxing club in Glasgow: "Far from being a useful and justifiable *sport*, amateur boxing is a dangerous, and often brutal, happening." He goes on to ask whether his nation is in a position to afford this type of disability production. It may be contended that the total damage produced by the boxing of a whole decade could not match the immediate devastation from one small hydrogen bomb, but such an argument ignores the baneful influence of boxing upon fans and spectators. For every onlooker who takes a genuine interest in the technique of the game, there must be many who consciously or subconsciously utilize boxing to foster their sadistic impulses. Otherwise, how can we explain the bloodthirsty howls with which a championship fight is so often punctuated? How else can we account for the specious arguments put forward to bolster up a pastime which will soon, we hope, be as obsolete as galley slaves or the chain gang?

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REFERENCES

1. Albaugh, C. H.: J. Internat. Coll. Surgeons **17**:191, 1952.

2. Carroll, E. J.: Am. J. M. Sc. **191**:706, 1936.

3. Graham, J. W.: Brit. M. J. **1**:219, 1955.

4. Jokl, E.: The Medical Aspects of Boxing, Pretoria, S. Africa, J. L. Van Schaik, Ltd., 1941.

5. Kaplan, H. A., and Browder, J.: J. A. M. A. **156**:1138, 1954.

6. Laurie, J. C.: Brit. M. J. **1**:227, 1955.

7. Maitland, H. S.: J. A. M. A. **91**:1103, 1928.

8. Parker, H. L.: J. Neurol. & Psychopath. **15**: 20, 1934.

9. Romino, J. D.: West Virginia M. J. **45**:19, 1949.

10. Sherrington, C. S.: The Integrative Action of the Nervous System, Ed. 2, Cambridge, England, Cambridge University Press, 1947.

11. Stallard, H. B.: Tr. Ophth. Soc. U. Kingdom **71**:58, 1951.

12. Symonds, C.: Proc. Roy. Soc. Med. **34**:289, 1941.

13. Taylor, R. B.: Brit. M. J. **1**:200, 1953.

14. Whiting, M. H.: Tr. Ophth. Soc. U. Kingdom **71**:58, 1951.

15. Winterstein, C. E.: Lancet **2**:719, 1937.

Flattened Anterior Chamber

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Flattened anterior chamber or absence of a formed anterior chamber is a complication of cataract surgery generally believed to be associated with a high incidence of aphakic glaucoma. While the incidence of vitreous loss, iris prolapse, and ocular infections has been reduced by refinements in anesthesia, wound closure, and antibiotic therapy, the occurrence of flat chamber still remains a problem.

Postoperative flat chamber, with its attendant danger of aphakic glaucoma, has been of great concern to the ophthalmic surgeon. Czermak [1] in 1897 recognized microscopically the closure of the chamber angle in aphakic glaucoma. A correlation between peripheral anterior synechiae and aphakic glaucoma was noted by Troncoso [2] in 1934. Kronfeld and Grossman,[3] McLean,[4] and, later, Meyer and Sternberg [5] indicated the relationship of delayed formation of the anterior chamber, peripheral anterior synechiae, and aphakic glaucoma. Sugar [6] attributed the delayed re-formation of the anterior chamber to poor wound closure associated with choroidal detachment and/or iris prolapse. Chandler and Johnson [7] attributed the delayed re-formation of the anterior chamber to a pupillary-block mechanism. In another publication dealing with the problem in flat chamber, Chandler [8] outlined his methods of therapy in cases with and without demonstrable wound leaks. Kronfeld,[9] who has contributed a great deal to the understanding of this subject, stated that "delayed or disturbed healing of the operative wound is the principal cause of delayed restoration of the chamber." He also, however, is inclined to the belief that a reduction in aqueous formation may play a part in explaining some aspects of flat chamber.

The experimental portion of our report consists of work done by one of us (J. B.), with the aid of H. Chinn,[10] a number of years ago, and we have reviewed these data with renewed interest as being pertinent to the problem of flat chamber. The clinical part of the work is recent and deals with observations on 500 consecutive cases of cataract extraction performed at Cook County Hospital. The last part of our paper deals with our concept of the mechanism of flat chamber formation. We have incorporated into this concept Kronfeld's suggestion of the significance of reduced aqueous flow and have drawn, in addition, from our own clinical and experimental impressions.

EXPERIMENTAL DATA

In 1940, Bellows and Chinn [10] demonstrated that prolonged drainage of the anterior chamber in dogs resulted in a marked reduction in aqueous formation, which they attributed to the blocking of the pupillary opening by the ball-valve action of the crystalline lens. In these experiments a 27-gauge needle was inserted into the anterior chamber at the most dependent part of the limbus and the aqueous was aspirated. Immediately after this, a cannula formed by the shaft of an 18-gauge needle was inserted through the same tract. The beveled edge faced the cornea, and the posterior surface lay parallel to the anterior surface of the iris. The regenerated

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aqueous flowed into tubes of known weights, which were changed at specified intervals. Clotting was prevented by the intravenous injection of an anticoagulant azo dye known as Chlorazol Fast Pink.

Results.—Immediately after paracentesis the dye became visible on the anterior surface of the iris, coloring the aqueous humor and indicating that plasmoid aqueous arises not only from the ciliary processes but also from the anterior surface of the iris.

With a uniform blood pressure it was shown that the rate of aqueous regeneration underwent three phases: a rapid flow of aqueous, with a precipitous drop during the first two hours; then a fairly constant rate for three to five hours, and, finally, a gradual tapering off to approach zero asymptotically (Chart 1).

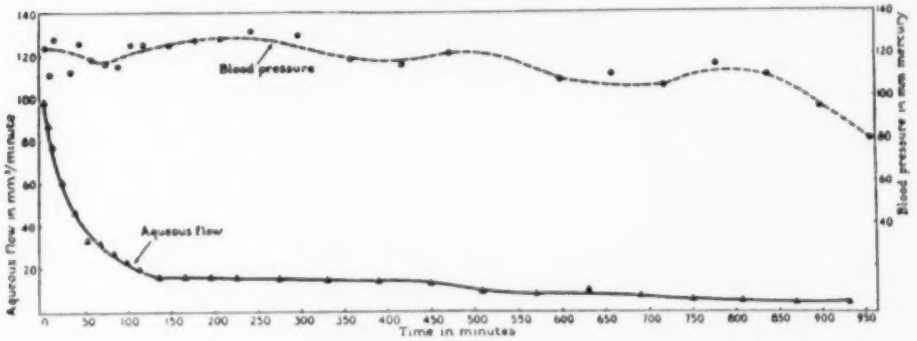

Chart 1.—Average rate of aqueous flow from normal eyes. From Bellows and Chinn.[10]

The changes in the specific gravity of the regenerated aqueous humor are also noteworthy. There is a rapid rise in specific gravity, which reaches a maximum in 5 to 25 minutes. In each instance a fall in specific gravity followed the rise. This rise and fall in some animals recurred several times, suggesting a rhythmic variation. A marked decrease in blood pressure produced a decline in the specific gravity and in the coloring of the aqueous (Chart 2).

Comment.—The explanation for the changes in the rate of flow and in the specific gravity is not entirely clear. The rate of flow does not depend upon the systemic blood pressure, because the flow decreases even with normal or rising blood pressure. It is unlikely that changes in the capillary permeability or vasoconstriction is important, because the specific gravity of the aqueous, which varies directly with the state of capillary permeability, rose during the time of the greatest decrease in the flow. The assumption based on the hypothesis that plasmoid aqueous is a true secretion and that exhaustion of the secretory cells causes the drop in the rate flow is indefensible, as the aqueous resumed its flow immediately after a posterior sclerotomy.

The most likely explanation for the decreasing flow of aqueous observed in these animals is the forward movement of the lens, producing a ball-valve action which obstructs the pupillary opening and the escape of the aqueous. Since the pressure in the anterior chamber equals that of atmospheric pressure and that in the posterior chamber remains relatively high, the lens dams up the opening more completely as the pressure in the posterior chamber increases. During this interval the flow of aqueous remains fairly constant, as only plasmoid aqueous arising from the anterior surface of the iris is able to escape. Gradually the ball-valve action dams back the aqueous from the ciliary processes, not only preventing its passage into the anterior chamber but decreasing its formation, owing to the back-pressure. Finally, the back-pressure becomes so great

as to affect not only ciliary vessels but also the vessels to the iris, causing a further decrease of the flow.

Support for this explanation is the observation that following posterior sclerotomy the flow of aqueous into the anterior chamber is accelerated. This, it may be assumed, is due to decreased pressure in the vitreous chamber, which permits the lens to resume a more normal position in relation to the iris and allows the aqueous to enter the anterior chamber. Further evidence to support the vitreous-obstruction theory is the repeated observation that the marked increase in aqueous flow noted when the blood pressure was increased, or when some other stimulus was applied in the early stages of the experiment, was seen to be greatly reduced in the late stages of the experiment, during which the obstruction of the pupil was most marked.

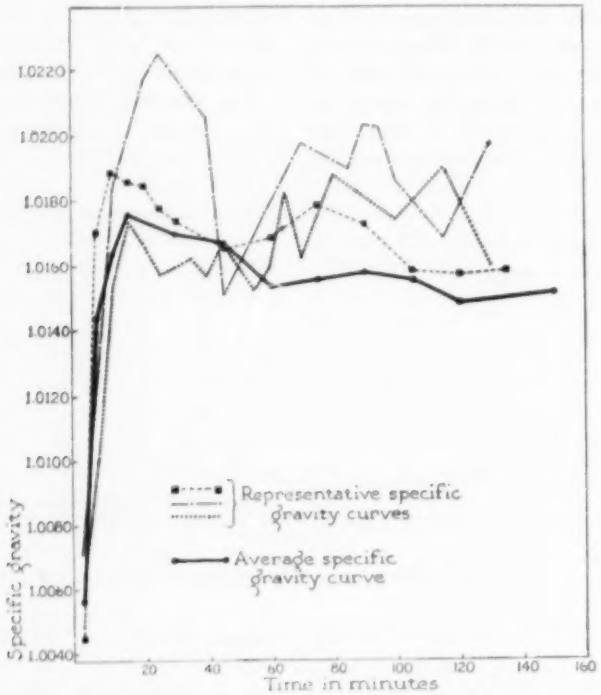

Chart 2.—Variations in the specific gravity of aqueous humor draining continuously from an open eye. From Bellows and Chinn.[10]

CLINICAL DATA

The clinical portion of this report is based on observations made in 500 consecutive cases of cataract extraction performed at the Cook County Hospital. Flattened anterior chambers were noted in 58 eyes. The object of this investigation was to determine whether the experimental data and interpretations would apply to clinical flattened anterior chambers. If postoperative flattened anterior chamber is caused by wound leakage, it should produce effects similar to those of an eye with a draining cannula in the anterior chamber. We hoped also to determine (1) the influences, if any, of various surgical techniques employed; (2) the influences, if any, of early or late surgical complications, and (3) the incidence and nature of glaucoma in eyes having had postoperative flattening of the anterior chamber.

TABLE 1.—*Relation of Surgical Technique to Incidence of Flat Chambers*

Operative Procedure	No. of Eyes	No. of Flat Chambers	Incidence, %
Keratome-scissors	292	29	10.0
Knife-scissors	208	29	13.9
McLean suture	322	36	11.5
Stallard suture	175	21	12.0
Complete iridectomy	370	37	10.0
Peripheral iridectomy	123	20	16.2
Intracapsular method	371	43	11.6
Extracapsular method	129	15	11.6
Forceps extraction	226	28	12.4
Erisophake extraction	260	30	11.5

Clinical observations of the status of the anterior chamber were made at the time of daily dressings of each postoperative cataractous eye. The exact degree of shallowness of the anterior chamber was not determined, but all eyes in which the anterior chamber was abnormally flat were included. Patients having this complication remained in the hospital until re-formation of the anterior chamber took place. After the patient's discharge from the hospital, individual follow-up studies were continued on an outpatient basis.

INFLUENCE OF SURGICAL TECHNIQUE UPON FLAT CHAMBER

In order to determine what effect, if any, various operative procedures employed in this series might have on the incidence of flat chamber, a number of comparisons were made (Table 1).

Type of Section.—The corneal section was made by the keratome-scissors method in 292, or in 58%, of the eyes. The incidence of flat chamber was 10% in these eyes. In 208, or in 42% of the eyes, the corneal section was made with a knife and usually enlarged with a scissors. Flat anterior chamber occurred in 13.4% of these eyes.

Type of Suture.—Two or three corneoscleral appositional sutures of the McLean type were employed in 322, or 64.4% of the eyes, while a single suture of the mattress-of-Stallard type was used in 175, or 35% of the eyes. The incidence of flat chambers in the two groups was 11.2% and 12.0%, respectively.

Iridectomy.—Complete iridectomy was performed in 370, or 74.0%, of the eyes, while 123, or 24.6%, of the eyes had one or more peripheral iridectomies. Flat anterior chamber occurred in 10.0% with complete iridectomy and in 16.2% with peripheral iridectomy.

Method of Extraction.—The intracapsular extraction was employed 371 times (74.2% of the eyes), and the extracapsular method, either intentional or unintentional, 129 times (25.8% of the eyes). The incidence of flat chamber in both groups was 11.6%.

Comment.—Wound leakage has been implicated frequently as a major factor in the production of flattened anterior chambers. If so, our findings indicate that the type of corneal section or the method of corneoscleral suturing employed in this series does not appear to influence the incidence of wound leakage and flattened anterior chamber.

The lower incidence of flattened anterior chamber in the group with complete iridectomy than in the group with peripheral iridectomy suggests that a complete iridectomy may afford a greater degree of protection against this complication. This protection is brought about by the greater ease with which the vitreous can plug up the small opening of the round pupil and peripheral iridectomy as compared with the larger opening of the complete iridectomy. The latter permits escape of aqueous from the posterior regions into the anterior chamber.

INFLUENCE OF SURGICAL COMPLICATIONS

The surgical complications were noted and tabulated. Table 2 illustrates that flattened anterior chamber ranks second to hyphema in frequency.

TABLE 2.—*Complications Occurring in 500 Consecutive Senile Cataract Extractions*

	No. of Cases	Per Cent
Hyphema	101	20.2
Iris prolapse	16	3.2
Infection	4	0.8
Uveitis	3	0.6
Flat chamber	58	11.6
Massive hemorrhage	3	0.6
Vitreous loss	50	10.0

TABLE 3.—*Relation of Other Complications to Flat Chamber*

	Flat Chamber (58 Eyes)	Normal Depth (442 Eyes)
Hyphema	15 (27.6%)	84 (18%)
Iris prolapse	2 (4%)	14 (3%)
Vitreous loss	1 (1.7%)	49 (11%)

Flat chamber was also associated in several eyes with other postoperative or surgical complications (Table 3).

Comment.—Flat chamber occurred more frequently in eyes having hyphema, which usually preceded the flat chamber. In this series iris prolapse was rather infrequent and was equally present in the two groups. In the two cases where iris prolapse was associated with flat chamber glaucoma developed. A striking absence of flat chamber in eyes having had vitreous loss at surgery is noted. In the one case in which it occurred an unintentional extracapsular extraction had been performed.

Results.—A total of 58 cases of postoperative flat anterior chamber occurred in the 500 cataract extractions studied. Fifty-one eyes were followed with periodic examinations from six months to three years. Seven eyes were followed from two to six months. All patients were subjected to an examination consisting of ophthalmoscopy, tonometry, biomicroscopy, determination of the corrected visual acuity, and, in most instances, gonioscopy.

TABLE 4.—*Early Type of Flat Chamber: Duration; Incidence of Glaucoma*

Duration, Days	No. of Flat Chambers	No. of Eyes Developing Glaucoma
1- 4	1	0
5- 8	10	3
9-12	8	2
13-16	5	0
17-25	4	0
26-47	3	1
Total	31	6

TABLE 5.—*Time of Appearance of Late Type*

No. of Days	No. of Cases
4	2
5	0
6	0
7	2
8	1
9	8
10	2
11	1
12	3
13	2
14	3
15	2

Flattening of the anterior chamber occurred early or late in the postoperative course. The early type was characterized by a delay in re-formation of the anterior chamber; the late type was characterized by a formed chamber, which after a variable period became flat.

Early Type (Delayed Re-Formation): Thirty-one eyes exhibited a flat anterior chamber present from the first postoperative dressing and lasting as long as 47 days. In all but four eyes of this group the anterior chamber re-formed spontaneously. With reference to these four cases, the anterior chamber was restored by repair of an iris prolapse in one case, by saline injection into the anterior chamber in one case, and by air injection and posterior sclerotomy in two cases. Six eyes in this early type developed aphakic glaucoma. Five of the six cases of aphakic glaucoma developed in those cases in which the anterior chamber remained flat between 5 and 12 days. It is noteworthy that if the condition persists beyond this time the incidence of aphakic glaucoma does not increase appreciably. Four of these six glaucomatous eyes had been associated with one or more of the following complications: hyphema, unintentional rupture of capsule during extraction, and iris prolapse.

Late Type (Secondary Loss of Chamber): Twenty-seven eyes had a formed chamber following surgery. After a period of 4 to 15 days, however, the anterior chamber became flat.

The late type of flat chamber most commonly occurred during the second postoperative week. The anterior chamber re-formed spontaneously in all but two eyes; in one, air injection and posterior sclerotomy were performed, and in the second, iris prolapse was repaired. Two eyes of the late type

developed glaucoma (Table 6), but both were associated with complications. In one case there was iris prolapse with vitreous loss, and in the other there had been unintentional extracapsular extraction and vitreous hemorrhage.

GENERAL COMMENT

On the basis of our experimental and clinical findings, our concept of the mechanism of flattened anterior chamber following cataract surgery can now be explained.

Upon removal of the lens, the hyaloid face of the vitreous and the iris approximate each other, the region occupied by the lens being now only a potential space. If the corneal wound is watertight, the regenerated aqueous escapes through the pupillary opening to fill the anterior chamber and normal aphakic depth is soon established. If, for some reason, the wound is not tightly closed, aqueous escapes. When this escape continues for only a short period and the wound then seals itself off, a flat chamber is not likely to result. When this leakage occurs over a period of five or six hours or more, however, a condition is established which is analogous to the previously described animal experimentation, in which prolonged drainage of the chamber was seen to cause a marked diminution in aqueous flow.* A wound leakage six hours or more in duration, sealed off either shortly afterward or much later, is the factor which starts into motion the following sequence of events: During the period of aqueous escape, a pressure gradient exists between the anterior and the posterior chamber, the pressure in the anterior chamber approaching atmospheric pressure and the pressure in the posterior segment remaining relatively higher. This pressure differential has a tendency gradually to draw the vitreous face forward and to cause it to press firmly against the iris and its openings, thus causing a partial obstruction to free passage of aqueous into the anterior chamber. With this impediment to the exit of aqueous from the posterior chamber, the pressure gradient increases, pressing the hyaloid and vitreous still more firmly against the pupil, so that eventually there is complete obstruction to the flow of aqueous.

TABLE 6.—*Late Type of Flat Chamber: Duration: Incidence of Glaucoma*

Duration, Days	No. of Cases of Flat Chamber	No. of Cases of Glaucoma
1- 4	6	0
5- 8	9	1
9-12	9	0
13-14	3	1

It is evident that once the pupillary and iridectomy openings have become obstructed, and it is not unreasonable to suppose that this requires not more than a few hours, there is then no longer the necessity of assuming a wound leak to account for the flat chamber, since the vitreous obstruction to the pupillary and iridectomy openings is sufficient reason for it. For many years, ophthalmologists have been puzzled at their inability to detect wound leakage in eyes having flat chambers. We offer for consideration the possibility that in many cases, although a transient wound leakage originally existed and resulted in the formation of pupillary block, the wound edges are well sealed at the time of the first 24-hour dressing. Actually, even in the presence of a frank wound opening, a demonstrable escape of aqueous should not be expected once the stage of obstruction has been reached.

When the dam-like effect of the hyaloid and the vitreous is in full operation, the accumulation of regenerated aqueous eventually results in a backward-pressure effect, which interferes with the circulation in the ciliary processes, causing a reduction in aqueous formation. Eventually, the circulation to the iris itself is involved, with a corresponding drop in the output of aqueous from its anterior surface. It is likely that the circulatory disturbance in the ciliary proc-

* The main difficulty in relating our postoperative cataractous eyes with the animal experimentation is that the lens was present in the experimental eye. We cannot see, however, that this offers any serious problem, since the vitreous body apparently acts in the same way as the lens in obstructing the pupillary opening.

esses, by backward extension, finally causes a similar stagnation and edema in the venous channels of the choroid. This leads to transudation into the suprachoroidal space and the elevation of choroid, a frequent accompaniment of flat chamber.

Since restoration of the anterior chamber occurs almost invariably, and even in the absence of any form of therapy, it must be assumed that the obstruction by the vitreous and the interruption of aqueous regeneration are temporary, lasting from a few hours to many days. The factors which cause the spontaneous lowering of pressure in the posterior chamber and thus allow the vitreous to fall back, with the resultant increased aqueous flow into the anterior chamber, are not known, and we can only speculate as to what this reversal mechanism might be. One possibility is that the reduction in the regeneration of aqueous finally tapers off to an extent that absorptive mechanisms in the posterior parts of the eye carry off more aqueous than is being formed. Mydriasis, gravity changes, and variations in blood pressure may also play some small part in the reversal of this condition.

To restate our concept, then, we are of the opinion that flat chamber is caused by a damlike effect of the vitreous brought into operation as a result of a pressure gradient between the anterior and the posterior segment, this being initiated by a transient wound defect; the resulting back-pressure in the posterior segment interferes with the uveal circulation, to diminish the aqueous regeneration, and finally leads to elevation of the choroid. Several considerations shall be mentioned in support of this argument. First of all, it offers a satisfactory explanation for the inability of the ophthalmologist to demonstrate a wound leak, even though all indications would point to such a defect being present. It also clearly explains the immediate flow of aqueous that is obtained after posterior sclerotomy, since the opening into the vitreous chamber causes a lowered pressure, which permits the vitreous body to shift back from its obstructing position in the pupil. We believe that, although it may be preferable, it is not essential to perform a sclerotomy at the site of choroidal elevation, since the main objective is achieved when an opening is made into the posterior segment. It is also noteworthy that flat chambers occur almost exclusively in cases where the hyaloid membrane remains intact, thus allowing the vitreous body to act as an obstructing wedge against the pupil; there need be no concern for flat chamber where the cataract extraction is complicated by a ruptured hyaloid membrane and vitreous loss. This observation is in agreement with the findings of Chandler † and is the basis for the broad vitreal incisions recommended by Shaffer [11] in desperate cases of malignant glaucoma due to pupillary obstruction. In our own experience in three cases of long-standing flattening of the anterior chamber which did not respond to the usual treatment, incision of the anterior face of the hyaloid and vitreous resulted in the immediate restoration of the anterior chamber. Also of importance is the fact that in our series of extractions, the incidence of flat chamber was far less in cases in which a complete iridectomy was performed than in those with a peripheral iridectomy or iridotomy. It seems reasonable to assume that the larger opening of a complete iridectomy could less easily be obstructed by the vitreous body than could the smaller area corresponding to a round pupil with a peripheral iridectomy. Chandler's classical description of shallowness of the anterior chamber and subsequent secondary glaucoma in aphakia is widely known, and his explanation that the mechanism involves a block between the anterior and the posterior segment is firmly established. Recently, Kronfeld has stated his belief that the reduction in aqueous formation which follows prolonged fistulation of the anterior chamber is a very likely factor in the mechanism of flat chamber. The prevailing idea would appear to be that two distinct and separate mechanisms operate to produce flattening, i. e., the form involving a leaking wound defect and that involving a pupillary-block mechanism. Our concept, embodying

† Chandler, P. A., in discussion on Shaffer.[11]

both these mechanisms, relates one to the other in a logical chain of events and offers, we believe, a single rational approach to the whole picture of flat chamber.

MANAGEMENT OF FLATTENED ANTERIOR CHAMBER

Prophylaxis.—Since it is known that flattened anterior chamber results from a leaking wound, either as a direct consequence or, as we believe, less directly, through a series of related events, it is obvious that a primary consideration is to secure a watertight wound upon the completion of surgery. The main objective of the surgeon in this regard should be to develop a technique of incision and suturing which will assure good closure in all cases. In our own experience, it does not seem to matter whether the incision is made with a keratome and scissors or with a von Graefe knife so long as the edges are of a fairly even contour and will readily fall back into their original position relative to each other. In our series of cases, the incidence of flattened anterior chamber was approximately the same with multiple McLean sutures as it was with a single Stallard suture. The chief function of suturing is to achieve good closure, and this depends not so much upon the type of corneoscleral suture used as upon its accurate placement, i. e., that it be of proper depth and achieve exact realignment. The suture should be tied securely to bring the edges into close contact, but not necessarily so tight that the cornea is distorted, as this may lead to buckling of the wound edges. The wound should, of course, be free of vitreous, iris, and capsular remnants. If the conjunctival flap has been of the fornix-based type, extra care should be taken to eliminate the possibility of inclusion of conjunctival tags in the wound. A complete iridectomy would seem to be of definite prophylactic value, for the reasons previously mentioned. Ideally, one should be able to see a refilling of the anterior chamber by the time the operative procedures are completed. Following surgery, every effort must be made to prevent the patient from straining, coughing, sneezing, and retching, as this violence may very well open the wound and cause flattening of the chamber. Premature removal of the sutures is to be avoided; when they are to be removed, they should be cut first, before any attempt is made to grasp them with the forceps.

Treatment.—Ordinarily the surgeon does not recognize the presence of a postoperative flattened chamber until the time of the first dressing, which is usually 24 hours following the surgery. If, at this time, due to poor suturing, iris prolapse, etc., an obvious gross wound defect exists, immediate surgical correction is indicated. If a wound defect cannot be detected, it is still possible that a small opening may exist, which, as a result of the pupillary block, does not seep aqueous. If after three or four days the chamber still remains flattened, then dilatation of the pupil may be tried, and occasionally will be beneficial. If there is no improvement, one may wish to use acetazoleamide (Diamox) in 250 mg. doses two or three times a day. This drug is now being employed extensively in cases of flat chamber, although, because of the frequency of spontaneous restoration of the chamber, it is still too early to evaluate its worth accurately. Among our own cases there have been several failures with acetazoleamide. If acetazoleamide is effective, its mechanism probably depends upon its ability to reduce the pressure in the posterior segment by further reducing the already diminished rate of aqueous regeneration.

If the restoration of the anterior chamber has not occurred by the fourth or fifth day, it is advisable to inject an air bubble into the chamber. The presence of an air bubble may alter the pressure relationship between the anterior and the posterior segment and thus allow aqueous to flow into the chamber again. If this measure fails, a posterior sclerotomy with injection of an air bubble into the anterior chamber has been the procedure employed by most ophthalmologists up to this time. This procedure is successful in a high percentage of cases. In the event the chamber still remains unformed, however, the surgeon should consider the incision of the an-

terior face of the vitreous. Although our experience with the last procedure has not been sufficient to permit us to make any definite claims, the operation would appear to be simple, and one meriting further investigation in view of the serious consequences of long-delayed re-formation of the chamber.

SUMMARY

The clinical entity of flattened anterior chamber is caused by a leaking wound which produces an abnormal pressure relationship between the anterior and the posterior segment of the eyeball. The result of this abnormal pressure relationship is the formation of a vitreous dam obstructing the flow of aqueous into the anterior chamber. The back-pressure resulting from this obstruction leads to edema and stagnation of the vessels in the ciliary body and the choroid, causing interruption in the regeneration of the aqueous humor and transudation into the suprachoroidal space, with elevation of the choroid. If the anterior chamber fails to reform spontaneously, and if a gross wound defect is absent, medical treatment is employed to relieve the abnormal pressure relationship. Failure of medical treatment necessitates one or more of the following surgical procedures, named in order of preference: injection of an air bubble, posterior sclerotomy, and an incision of the anterior face of the vitreous.

REFERENCES

1. Czermak, W.: Die augenärztliche Operationen, Vienna, C. Gerold's Sohn, 1898.

2. Troncoso, M. U.: Gonioscopy, Tr. Internat. Cong. Ophth. **1**:25, 1934.

3. Kronfeld, P. C., and Grossman, E. E.: Relation of Gonioscopic Findings to Incidence of Secondary Glaucoma in Operative Aphakia, Tr. Am. Acad. Ophth. **45**:184, 1941.

4. McLean, J. M.: Gonioscopy in Glaucoma Operations, Tr. Am. Acad. Ophth. **45**:176, 1941.

5. Meyer, S. J., and Sternberg, P.: Secondary Glaucoma After Cataract Extraction, Tr. Am. Acad. Ophth. **54**:326, 1949-1950.

6. Sugar, H. S.: The Glaucomas, St. Louis, C. V. Mosby Company, 1951.

7. Chandler, P. A., and Johnson, C. C.: A Neglected Cause of Secondary Glaucomas in Eyes in Which the Lens Is Absent or Subluxated, Arch. Ophth. **37**:740, 1947.

8. Chandler, P. A.: Complications After Cataract Extraction: Clinical Aspects, in Symposium on Cataract Extraction, Tr. Am. Acad. Ophth. **58**: 382, 1954.

9. Kronfeld, P. C.: Delayed Restoration of Anterior Chamber, Am. J. Ophth. **38**:453, 1954.

10. Bellows, J. G., and Chinn, H.: Regeneration of the Aqueous, Arch. Ophth. **24**:1144, 1940.

11. Shaffer, R. N.: Role of Vitreous Detachment in Aphakic and Malignant Glaucoma, Tr. Am. Acad. Ophth. **58**:217, 1954.

Fuchs' Syndrome of Heterochromic Cyclitis

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Fuchs' syndrome of heterochromic cyclitis is a commoner ocular disorder than has generally been recognized in this country. Most of the reports on the disease are to be found in the European literature.* Not only have American observers † failed largely to identify the syndrome, but in extensive surveys ‡ of patients with uveitis they have omitted it from consideration in their attempts at differential diagnosis. At the University of California Hospital,§ however, better than 2% of some 750 cases of uveitis surveyed between 1949 and 1955 were clear-cut examples of this interesting syndrome. Most of them had been referred to the clinic for diagnosis.

The purpose of this paper is to point out the frequency with which Fuchs' syndrome occurs in the western part of the United States and to suggest the importance of recognizing it. If a case of uveitis can be identified as Fuchs' syndrome at the first examination, or at least early in the study, a great deal of fruitless effort, time-consuming and expensive, can be avoided. In spite of the incurability of the disease, moreover, the prognosis is good and the patient can be so assured when the diagnosis is made.

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* References 1 through 12.

† References 13 through 20.

‡ References 18 and 19.

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CLINICAL PICTURE

Fuchs' heterochromic cyclitis appears most frequently in the third or fourth decade of life. It has an insidious onset and a very long, mild, chronic course. There are no gross signs of inflammation. The eye is white, and the patient is usually unaware of any trouble until vitreous opacities or lens opacification, a late development, interferes with vision. The disease is thus usually present a long time before it is discovered. Some of the more observant patients may note the heterochromia, which develops very gradually.

Signs.—The typical fully developed case presents the following classical triad of signs: (1) heterochromia, (2) cyclitis, and (3) cataract.

1. Heterochromia: The difference in the color of the irides may be marked (Fig. 1*A*) or may be very slight. In the opinion of some observers, including ourselves, it may even be absent. The heterochromia, which increases very slowly over the years, is more noticeable when the irides are blue. Typically the hypochromic eye is the affected eye, but if the patient is blond it may be the darker eye that is involved. In rare cases, first noted by Houwer,[11] François,[12] and Franceschetti,[13] both eyes are involved. Under the biomicroscope the affected iris looks smooth and less than normally transparent, and the radial markings of the pupillary zone are not as prominent as they are in the normal iris

(Fig. 1*B* and *C*). The pigment layer may have a moth-eaten appearance (Fig. 2). There are never any posterior synechiae.

None of the cases in our series gave a history of congenital heterochromia, nor has any one of us encountered in the clinic or in private practice any case of congenital heterochromia that has later developed Fuchs' syndrome of heterochromic cyclitis. This is in distinct contrast to Franceschetti's [12] finding that heterochromia was congenital in 14.5% of his series.

2. Cyclitis: The one constant feature of this syndrome is the very mild, chronic cyclitis. The presence of stringy or dust-like floaters in the anterior vitreous, flare and cells in the aqueous, and keratic precipitates

Fig. 4 (Case 4, H. C.).—R. E.: cataract and hypochromia.

attest a mild inflammatory process. According to Franceschetti,[12] the vitreous opacities appear biomicroscopically as white dots rather than as the brownish ones seen in other types of uveitis. The aqueous flare and cells are always minimal. The keratic precipitates which are seen typically in the pupillary area and the lower portion of the cornea, are a constant finding and are characteristically small or medium in size, white in color, sharply circumscribed, and never confluent. In between them fine filaments can be seen (Fig. 3).

3. Cataract: Early in the disease the lens is clear. The cataract, which is a complicated type that starts in the posterior cortex beneath the capsule, forms as a result of the long-standing cyclitis (Fig. 4). This late development limits the value of the cataract as a diagnostic sign.

Peripheral Choroiditis: In addition to these three classical signs, peripheral choroiditis is occasionally observed. It may be guessed that it is often present but missed because the peripheral retina is rarely examined.

Complications.—The only serious complication is secondary glaucoma. Franceschetti [12] found that 13% of his cases developed glaucoma; he felt that the bilateral cases were more likely to do so than the typical unilateral case, but his series was too small for the figures to have any significance. No glaucoma was seen in connection with our series, since most of the cases were referred for diagnosis only and were not followed for any length of time.

DIAGNOSIS

Like other syndromes, Fuchs' heterochromic cyclitis can be diagnosed when some of its characteristic manifestations are missing. According to several observers, and in our opinion, the heterochromia itself is not a constant sign and the disease can be identified in its absence. According to this point of view, it is the character and course of the cyclitis rather than the heterochromia which identify the disease, i. e., the quiet white eye which on examination shows several or all of the characteristic signs of an extremely mild iridocyclitis: minimal aqueous flare and cells; vitreous opacities; small, white, discrete keratic precipitates, and total absence of synechiae. On this basis Franceschetti [11] suggested that the disease might better be called simply "Fuchs' syndrome."

As indicated above, the classical sign of cataract cannot be relied upon for diagnosis, since it is typically a late development.

Amsler and Verrey [3] reported an interesting finding which Auvert and Lavat,[9] François,[12] and Franceschetti [12] regard as pathognomonic of Fuchs' heterochromic cyclitis. They found that when an anterior chamber puncture was made in an eye affected with this disease a hemorrhage occurred in the

Fig. 1A.—Case 11, V. W.

Fig. 1B (same case).—R. E.: normal, blue iris.

Fig. 1C (same case).—L. E.: hypochromic iris, less transparent and lighter blue than in R. E.

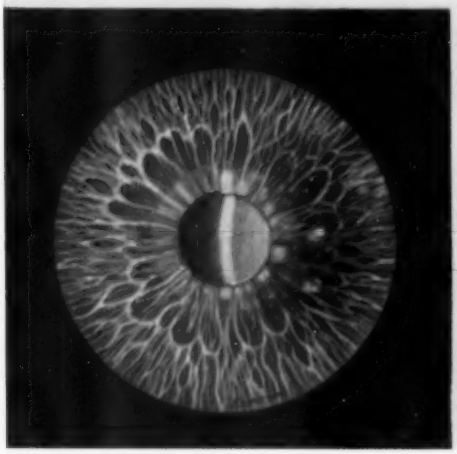


Fig. 2 (Case 16, R. C.).—R. E.: atrophy of pigment layer of iris.

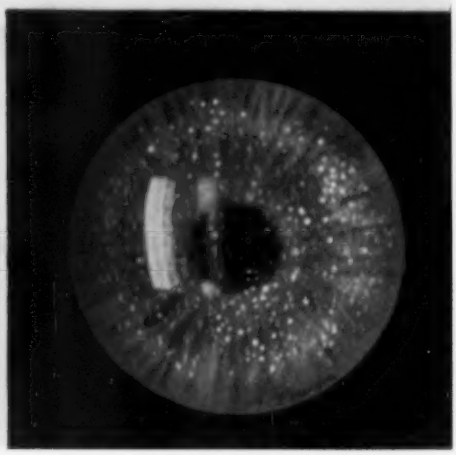


Fig. 3 (same case).—R. E.: keratic precipitates.

angle. No attempt was made in our study to confirm this finding.

Fuchs' syndrome is readily differentiable from the heterochromias secondary to uveitis of other etiology. In these other heterochromias there is marked patchy atrophy of the iris stroma, and often there are signs of posterior synechiae. These are never seen in Fuchs' syndrome unless it is complicated by secondary glaucoma. As compared with the other types of uveitis in which heterochromia occurs, moreover, Fuchs' syndrome is the only type that follows a benign course.

Franceschetti [13] has called attention to the fact that when secondary glaucoma is present in an eye with heterochromic cyclitis, the syndrome of glaucomatocyclitic crises must be considered in the differential diagnosis. In the nine cases of this syndrome reported by Posner and Schlossman,[20] three had definite heterochromia. The relationship, if any, of Fuchs' heterochromic cyclitis to the Posner-Schlossman syndrome is not known. The increased tension in the syndrome of glaucomatocyclitic crises is self-limited, and the keratic precipitates usually disappear when the tension returns to normal.

ETIOLOGY

The etiology of heterochromic cyclitis is unknown. Fuchs thought the disease was due to some unidentified toxin. Since then many theories have been advanced. Infection with tuberculosis,‖ circulatory disturbances,¶ dysraphia,# and sympathetic nervous system disturbances * have all been suggested. Franceschetti found some evidence of status dysraphicus in 45% of his heterochromic cyclitis series but stated that with one exception the signs were very slight.

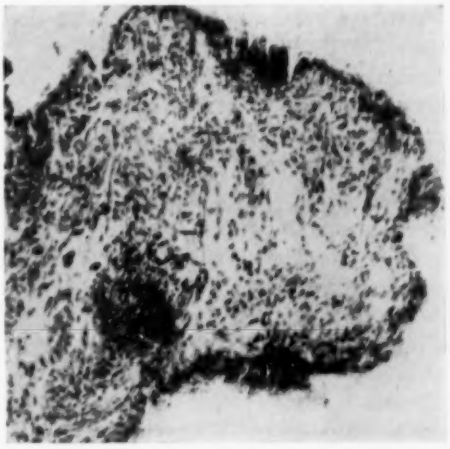
Of the other possibilities, perhaps the theory of sympathetic nervous system disturbance has the most adherents today. François [5] has shown that cases of Fuchs' syndrome exhibit a definite sympathetic paresis. He has hypothesized that heterochromic cyclitis is not an inflammation but a degeneration that follows paresis of the sympathetic nervous system. He does not believe it to be due to sympathetic paralysis, however, since patients with heterochromic cyclitis rarely, if ever, show signs of sympathetic nervous system paralysis. In this connection, Calmettes and associates [10] reported a case in which Horner's syndrome followed stellate ganglionectomy and heterochromic cyclitis developed in the same eye. This complication could, of course, have been purely coincidental.

In the course of the present study no new light was shed on the problem of etiology.

PATHOLOGY

The iris shows a decrease in the number of stromal melanocytes, with patchy depigmentation of the posterior pigment layer (Fig. 2; Clinical Picture). The vessels in the two specimens available in our laboratory do not show thickening of their walls. One specimen shows a deposition of brown pigment on the anterior border layer, probably laid down by phagocytes. The stroma shows

Fig. 5 (Case 17, EP-55-122).—Photomicrograph of iris.



‖ References 14 and 16.

¶ Reference 3. Weill (1904), cited by Duke-Elder,[21] p. 1407.

Reference 11. Passow, A., cited by Franceschetti.[13]

* Reference 7. Scalinci (1915), cited by Duke-Elder,[21] p. 1407.

a moderate diffuse fibrosis and a diffuse infiltration of lymphocytes and plasma cells (Fig. 5).

The ciliary body usually shows stromal fibrosis, with muscular atrophy. Areas of focal cyclitis and peripheral choroiditis may exist, corresponding to the lesions observed in some clinical cases. Those cases complicated by glaucoma show marked atrophy of the iris, ciliary body, and retina and glaucomatous cupping of the disc. In the one specimen we have, which was removed after the development of absolute glaucoma, the angle is open and the trabecular meshwork shows severe fibrosis.

TREATMENT AND PROGNOSIS

There is no known treatment for heterochromic cyclitis. Corticotropin and the adrenocorticosteroid hormones, whether administered topically or parenterally, are of no value. The cataracts are removed easily, and the eye tends to respond well to surgical trauma in spite of the active cyclitis. The glaucoma that often occurs as a complication is treated by the usual methods. Only one of us has any personal knowledge of this complication; his experience was with three cases, all of which proved extremely refractory to treatment.

In spite of the incurability of the disease, and in spite of the inevitable cataract and the possibility of glaucoma, the prognosis of Fuchs' syndrome may be called good. Unless glaucoma develops, the disease follows its benign course without incident. There is no serious impairment of vision except by the cataract, and the cataract yields readily to surgical intervention.

ANALYSIS OF CASES

For the purposes of this study, the records of 29 cases of heterochromia were drawn from the files of the Uveitis Clinic of the University of California Hospital. These represented all the records in which heterochromia had been noted in the course of surveying approximately 750 consecutive cases of uveitis since December, 1949, plus 4 cases without heterochromia which were diagnosed as "Fuchs' syndrome."

All the records contained the following data: (1) brief medical history and detailed ophthalmic history; (2) complete physical examination; (3) detailed examination of the eyes, including slit-lamp biomicroscopy and ophthalmoscopy with pupils dilated; (4) skin tests, including the tuberculin, Frei, toxoplasmin, coccidioidin, histoplasmin, and brucellergin tests; (5) serologic tests, including the Toxoplasma dye test, the Toxoplasma complement fixation test, the Brucella agglutination and complement fixation tests, the Q-fever complement fixation test, and the Kline and Kahn tests for syphilis; (6) neutralization test for toxoplasmosis; (7) white blood cell and differential counts; (8) sedimentation rate determination, and (9) roentgen chest examination and special films of joints, skull, and phalanges when indicated by the history or the physical examination.

TABLE 1.—*Types of Heterochromic Cyclitis Studied*

	No. of Cases
Fuchs' syndrome of heterochromic cyclitis	17
"Fuchs' syndrome" without heterochromia	4
"Bilateral Fuchs' syndrome of heterochromic cyclitis"	2
Heterochromia secondary to uveitis of other etiology	6
Total	29

The types of heterochromic cyclitis included in the 29 cases are listed in Table 1.

Fuchs' Syndrome of Heterochromic Cyclitis.—There were 17 cases of clear-cut Fuchs' heterochromic cyclitis (Table 2). All three authors concurred in this opinion after examining the patients independently. In each of these cases the heterochromia was readily detectable when the patient was examined in daylight. In each, the course was typical, there were no synechiae, and all or most of the distinguishing signs of the characteristic cyclitis were present. In 12 of the 17 cases there were complicated cataracts. Most of the patients had some visual complaints, such as blurred vision or spots before

their eyes, which were related to the cataract or to the presence of vitreous opacities.

Table 2 was compiled from the records of the first survey examination, and at that time no aqueous cells or flare and no vitreous opacities were noted in Patient 12 (B. W.). This patient was a student nurse whom we were able to observe at intervals for three years, however, and at the later examinations these signs were in evidence.

patients had no visual complaints. The keratic precipitates, aqueous flare and cells, and vitreous opacities had been discovered in the course of routine eye examinations and were interpreted as evidence of "Fuchs' syndrome." In one case there was a complicated cataract.

Probable Cases of "Bilateral Fuchs' Syndrome."—Two cases believed to be examples of the so-called "bilateral Fuchs' syndrome

TABLE 2.—*Fuchs' Syndrome of Heterochromic Cyclitis*

Patient	Sex	Age	K. P.	Flare	Cells	Vitreous Opacities	Cataract
1 H. C.	F	50	+	±	Occ.	+	+
2 R. M.	M	27	—	±	+	+	+
3 C. P.	M	31	+	+	Occ.	+	+
4 T. T.	M	59	+	—	+	+	—
5 D. R.	M	55	+	±	Occ.	?*	+
6 H. G.	F	37	+	±	Occ.	—	—
7 D. W.	M	43	+	—	—	+	+
8 R. S.	M	13	+	±	Occ.	?*	+
9 L. F.	M	21	+	+	+	?*	+
10 C. W.	M	31	+	+	+	+	+
11 V. W.	F	26	+	±	Occ.	—	+
12 B. W.	F	20	+	—	—	—	—
13 H. S.	M	37	+	+	+	+	+
14 L. C.	F	34	+	+	+	+	—
15 C. G.	M	21	+	—	+	+	—
16 R. C.	M	38	+	±	Occ.	?*	+
17 D. D.	M	31	+	+	+	?*	+

* Vitreous not visible because of cataract.

TABLE 3.—*Fuchs' Syndrome Without Heterochromia*

Patient	Sex	Age	K. P.	Flare	Cells	Vitreous Opacities	Cataract
1 E. A.	F	60	+	+	+	+	—
2 G. R.	M	47	+	+	+	+	+
3 L. P.	F	28	+	±	+	+	—
4 V. O'L.	M	44	+	+	+	+	—

The age range of the patients in this group corresponds to that of other series reported in the literature. The sex distribution is not the usual 1 : 1, but the series is too small for such a variation to have any significance.

"Fuchs' Syndrome" Without Heterochromia.—Four cases of "Fuchs' syndrome" without heterochromia are listed separately in Table 3. None of these patients had detectable heterochromia, but the other characteristic signs of the cyclitis were present. There was no gross evidence of inflammation in any of the eyes, and two of the four

of heterochromic cyclitis" are listed separately in Table 4. It is suggested that "bilateral . . . heterochromic cyclitis" is a contradiction in terms. If the proposition that the disease is not always heterochromic is accepted, however, and the name "Fuchs' syndrome" is adopted as more accurately descriptive than "Fuchs' syndrome of heterochromic cyclitis," the disease involving both eyes might then more appropriately be termed "bilateral Fuchs' syndrome."

Both patients in Table 4 had had their disease many years. The eyes had never been

TABLE 4.—*Probable Examples of "Bilateral Fuchs' Syndrome"*

Patient	Sex	Age	K. P.	Flare	Cells	Vitreous Opacities	Cataract	Fundus
1 N. Z.	F	38	O. U. +	O. U. +	O. U. +	O. D. ?*	O. D. Mature	O. D. ?*
						O. S. —	O. S. Postsub-caps.	O. S. Clear
2 R. C.	F	29	O. D. +	O. D. ±	O. D. ±	O. D. +	O. D. Aphakic	O. D. Clear
			O. S. —	O. S. —	O. S. —	O. S. +	O. S. Postsub-caps.	O. S. Clear

* Vitreous and fundus not visible because of cataract.

TABLE 5.—*Results of Skin Tests of Patients with Fuchs' Syndrome**

Patient	Toxoplasmin	Brucellergin	Coccidioidin	Frei	Histoplasmin	Tuberculin
1 H. C.	+	—	—	—	—	+
2 R. M.	+	—	—	—	—	—
3 C. P.	—	+	—	—	—	—
4 T. T.	—	—	+	—	+	—
5 D. R.	—	—	—	—	—	+
6 H. G.	—	—	—	—	—	+
7 D. W.	—	+	—	—	+	+
8 R. S.	—	—	—	—	—	—
9 L. F.	—	—	—	—	—	+
10 C. W.	—	+	—	—	—	+
11 V. W.	—	—	—	—	—	—
12 B. W.	—	—	+	—	—	—
13 H. S.	—	—	—	—	—	—
14 L. C.	—	—	—	—	—	—
15 C. G.	—	—	—	—	—	—
16 R. C.†	..	..	..	..	..	..
17 D. D.	—	—	—	—	—	+
18 E. A.	—	—	—	—	—	—
19 G. R.	—	—	—	—	—	+
20 L. P.	—	—	—	—	+	+
21 V. O'L.	—	—	—	—	—	+
22 N. Z.	—	—	—	—	—	+
23 R. C.	—	—	—	—	—	—

* From Tables 2, 3, and 4.
† No skin tests performed.

congested, and the irides showed no color difference and were free of any synechiae. The clinical picture and course in both cases were highly suggestive of heterochromic cyclitis, and the disease was so considered by us.

Results of Skin Tests of Patients with "Fuchs' Syndrome" (Tables 2, 3, and 4).—In Table 5 the positive skin tests of the 23 cases listed in Tables 2, 3, and 4 are recorded. The tuberculin test was positive in 11 cases, or in roughly one-half of the series. This corresponds roughly to the rate of positive tuberculin tests for the general population in this area, however, and is therefore without significance. In no other instance did the results of the laboratory tests make a contribution toward any sort of etiologic diagnosis.

Heterochromia Secondary to Uveitis of Other Etiology.—There were six cases of heterochromia in this series that were definitely not examples of Fuchs' syndrome (Table 6). The differentiation was based on the biomicroscopic picture of the iris, which showed patchy loss of substance in the stroma, and on the presence of synechiae, large chorioretinal lesions, large confluent keratic precipitates, and excessive signs of congestion and activity. Atrophy of the iris stroma was recorded in all but Case 6. That the latter was clearly not a case of Fuchs' syndrome, however, was evident from the patient's history of numerous acute exacerbations over a 10-year period.

There were, no doubt, many other patients surveyed in the Uveitis Clinic during this period that had heterochromia secondary to

TABLE 6.—*Secondary Heterochromia*

Patient	Sex	Age	K. P., Type	Iris Atrophy
1 J. B.	M	42	Large, crenating	Stromal, patchy, severe
2 J. H.	F	69	Large, crenating	Stromal, patchy
3 E. C.	F	33	Small	Stromal
4 E. P.	F	54	Finely pigmented	Stromal
5 R. E.	F	39	Small	Stromal
6 C. W.	F	45	Small	Not noted

uveitis of one etiology or another. In these unidentified cases, however, the heterochromia either was not noticed at all by the examiner, since it is often very slight, or, if noticed, was regarded as inconsequential and not noted on the record. In any event, this search of the files for examples of Fuchs' syndrome uncovered only the six cases of secondary heterochromia listed in Table 6.

SUMMARY AND CONCLUSIONS

Fuchs' syndrome of heterochromic cyclitis, a clinical entity of unknown etiology, can usually be readily diagnosed from gross examination of the color of the irides in daylight and from biomicroscopic examination of the affected eye.

In the uveitis survey conducted by the staff of the Francis I. Proctor Foundation for Research in Ophthalmology and the Department of Ophthalmology at the University of California Hospital, the incidence of Fuchs' syndrome of heterochromic cyclitis was better than 2%. In a series of 750 consecutive cases of uveitis, 17 clear-cut examples of the disease were identified.

Four additional cases which followed the course and exhibited all the distinguishing signs of the characteristic cyclitis, but in which there was no heterochromia, indicated that heterochromia is not a constant sign of the disease and that it can be diagnosed on the basis of the character and course of the cyclitis.

In two otherwise typical cases both eyes were involved. These were regarded as examples of "bilateral Fuchs' syndrome."

If the 4 cases without heterochromia and the 2 bilateral cases were correctly identified as examples of Fuchs' syndrome, there were then a total of 23 cases of this disease in the series, or 3% of the 750 cases of uveitis.

The recognition of Fuchs' syndrome is important in the differential diagnosis of uveitis. If it is recognized promptly, much time and expense can be saved both the examiner and the patient, since none of the tests made in the usually exhaustive work-up of a case of uveitis is of any value in the diagnosis or management of this entity.

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REFERENCES

1. Fuchs, E.: Über Komplikationen der Heterochromie, Ztschr. Augenh. **15**:191-212, 1906.

2. François, J.: L'Hétérochromie irienne de Fuchs, Ann. ocul. **179**:559-577, 1946.

3. Amsler, M., and Verrey, F.: Hétérochromie de Fuchs et fragilité vasculaire, Ophthalmologica **111**:117-181, 1946.

4. Raimondo, N.: Eterocromia di Fuchs con glaucoma: Considerazioni pathogenetiche, Ann. ottal. e clin. ocul. **74**:423-435, 1948.

5. François, J.: Contributions à l'étude de l'hétérochromie de Fuchs et de ses troubles pupillaires, Ann. ocul. **182**:585-596, 1949.

6. François, J.: Études pupillaires dans l'hétérochromie de Fuchs, Bull. Soc. belge opht. **91**:154-165, 1949.

7. Matteucci, P.: Considérations pathogéniques sur l'hétérochromie de Fuchs, Bull. et mém. Soc. franç. opht. **63**:220-224, 1950.

8. Auvert, B., and Lavat, J.: Hétérochromie de Fuchs et ponction de la chambre antérieure, Ann. ocul. **185**:810-812, 1952.

9. Paufique, L., and Chavanne, H.: Bull. Soc. opht. France, pp. 404-406, April, 1953.

10. Calmettes, M. L.; Deodati, and Amalric: Rev. oto-neuro-opht. **25**:399-400, 1953.

11. Houwer, A. W. M.: Bilateral Heterochromia Iridis, Ophthalmologica **127**:440, 1954.

12. François, J.: Fuchs' hétérochromie, Ann. ocul. **187**:255-272, 1954.

13. Franceschetti, A.; Heterochromic Cyclitis (Fuchs' Syndrome), Am. J. Ophth., to be published.

14. King, C.: Tuberculous Iridocyclitis as a Cause of the Heterochromia of Fuchs, Tr. Am. Ophth. Soc. **25**:380-412, 1927.

15. Gradle, H. S.: Heterochromia Iridis with Cyclitis and Cataract, Am. J. Ophth. **12**:547-557, 1929.

16. Lloyd, R. T.: Heterochromia and Allied Conditions with Case Reports, Am. J. Ophth. **14**: 287-299, 1931.

17. Edgerton, A. E.: Heterochromia and Cataract: Report of a Case, Am. J. Ophth. **16**:1076-1079, 1933.

18. Guyton, J. S., and Woods, A. C.: Etiology of Uveitis, Arch. Ophth. **26**:983-1018, 1941.

19. Woods, A. C., and Guyton, J. S.: Role of Sarcoidosis and of Brucellosis in Uveitis, Arch. Ophth. **31**:469-480, 1944.

20. Posner, A., and Schlossman, A.: Syndrome of Unilateral Recurrent Attacks of Glaucoma with Cyclitis Symptoms, Arch. Ophth. **39**:517-535, 1948.

21. Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. II, St. Louis, C. V. Mosby Company, 1938.

Long-Term Acetazoleamide (Diamox) Administration in Therapy of Glaucomas

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The lowering of intraocular pressure by the systemic administration of acetazoleamide (Diamox) [1] and other carbonic anhydrase inhibitors * has stimulated rather widespread interest in the use of these agents in the therapy of the glaucomas.†

Considerable evidence has been accumulated to suggest that the mode of action of these pressure-lowering agents is a partial suppression of secretion of the aqueous humor.[4] This hypothesis was based primarily upon tonographic and fluorescein-appearance-time data. Thus, acetazoleamide induced a fall in intraocular pressure without change in facility of outflow and associated with a delay in the appearance of fluorescein. Confirmatory evidence for this thesis has been obtained recently by measuring the change in rate of turnover of test substances in the eye and the alterations in the composition of the aqueous humor following acetazoleamide administration.‡ Of great theoretical significance have been the findings of inhibition of the carbonic anhydrase of the ciliary body by acetazoleamide [5] and reduction in the excess of bicarbonate in the ocular fluids as a result of such inhibition.‡

There is general agreement that short-term acetazoleamide administration is a most effective adjunct to other means of therapy in the treatment of the acute primary and secondary glaucomas. Thus, satisfactory lowering of intraocular pressure was reported in approximately 85% of a consecutive series of 380 eyes suffering from various types of glaucoma.§

From the outset it was tempting to speculate about the feasibility of continued administration of acetazoleamide in patients

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* Becker, B.: Unpublished observations, 1954.

† References 2 and 3. Thorpe, H. E.: Carbonic Anhydrase Inhibitor as a Therapeutic Agent in Ophthalmology, report presented at a meeting of the Association for Research in Ophthalmology, Eastern Division, Philadelphia, February, 1954. Becker, B.: Short-Term Administration of Acetazoleamide (Diamox) in the Therapy of the Glaucomas, presented at the International Congress of Ophthalmology, New York, Sept. 20, 1954.

‡ Becker, B.: Effects of Diamox on the Composition of the Rabbit Aqueous Humor, presented at the meeting of the Association for Research in Ophthalmology, June 8, 1955.

§ Becker, B.: Short-Term Administration of Diamox in the Therapy of the Glaucomas, presented at the International Congress of Ophthalmology, Sept. 20, 1954.

with chronic glaucoma.[1] The present study was undertaken in order to obtain more information about ocular and systemic toxicity, as well as the effectiveness of such therapy. It now appears firmly established that selected patients with otherwise uncontrolled glaucoma can be maintained on acetazoleamide for periods of over 18 months without loss of vision or field and without significant systemic or ocular toxicity. Unfortunately, this is not true for all patients suffering from glaucoma. It is the purpose of this report to summarize the results of an attempt to maintain 70 patients with uncontrolled chronic glaucoma on around-the-clock acetazoleamide for periods of over six months.

METHODS

A. Selection of Patients.—The patients included in this series were selected from the Eye Clinic of the Department of Ophthalmology, Washington University School of Medicine, and from private patients referred to the Department by members of its visiting staff. Of primary interest for this series were patients with open-angle glaucoma not surgically treated, uncontrolled on miotic therapy, and either losing visual field or with very small residual fields. Forty such patients were started on acetazoleamide therapy, in addition to continuing their miotic regimen. Ten more patients with open-angle glaucoma, uncontrolled on miotics after surgical procedures, were included in the series. In addition, 10 patients with chronic secondary glaucoma and 10 patients with chronic narrow-angle glaucoma were subjected to similar treatment. The latter groups consisted of patients who had far-advanced disease and who had been subjected to multiple unsuccessful operations or were reluctant to undergo surgery on the remaining eye after a disastrous result in the first eye. It is important to emphasize that only those patients who responded adequately to initial acetazoleamide therapy were included in the chronic series.

All patients were followed closely for ocular and systemic toxicity. In addition to careful eye examinations, repeated blood counts and urinalyses were performed.

B. Dosage of Acetazoleamide.—Wherever possible, patients were admitted to the hospital for 7 to 10 days of study with repeated tonograms and measurements of intraocular pressure around the clock. Dosage and frequency of administration of acetazoleamide were adjusted on an individual patient basis, i. e., enough to control intraocular pressure at all hours of the day and night with a minimum of side-effects.

Diamox ‖ was administered in divided doses every four to six hours to a total of 250-2000 mg. per day. The average dose necessary to control adult patients was 250 mg. every six hours. After it was established that "delayed action" Diamox ‖ usually acted 6 hours after oral administration, the drug was more conveniently given as 250 mg. of regular Diamox and 250 mg. of "delayed action" Diamox every 12 hours.

C. Other Drugs Used.—In several instances, ammonium chloride in doses of 1-2 gm. every six hours was found to potentiate the pressure-lowering effects of acetazoleamide. Potassium chloride, in doses of 1 gm. three times a day, was moderately successful in relieving side-effects in some patients. Since the pressure-lowering effects of acetazoleamide and miotics are additive,¶ acetazoleamide was used in conjunction with miotics (usually pilocarpine) in all patients in this series.

RESULTS

A. Criteria for Success.—Successful control of glaucoma was arbitrarily set as follows:

1. Maintenance of intraocular pressure in both eyes below 30 mm. Hg at all measurements
2. No loss of vision or visual field in either eye
3. No intolerable side-effects
4. Therapy continued for a minimum of six months with adequate follow-up

Any patient failing to meet one of these criteria was classified as a failure.

B. Open-Angle Glaucomas.—Since there was no difference in success rate between patients with open-angle glaucoma not surgically treated (25 of 40) and those with eyes subjected to previous surgery (6 of 10), all 50 cases of open-angle glaucoma are grouped together in Table 1. It is seen that

‖ The regular Diamox and the Diamox with formalinized gelatin coating ("delayed action" Diamox) used in this series were supplied through the courtesy of Dr. James D. Gallagher, of the Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

¶ Becker, B.: Evaluation of Glaucoma Therapy by Tonography, presented at the Symposium on Aqueous Flow, International Congress of Ophthalmology, New York, Sept. 21, 1954.

31 patients (62%) with previously uncontrolled open-angle glaucoma have been successfully treated with acetazoleamide for more than six months. Seventeen of these successes have been followed for periods of over one year.

Thirteen of the 19 failures were on the basis of intolerable side-effects. In only six patients (12% of this group) was therapy discontinued because of inadequate control of intraocular pressure (Table 2).

TABLE 1.—*Results of Long-Term Acetazoleamide Therapy in Chronic Glaucomas*
(70 patients treated for 6 to 15 months)

Diagnosis	No.	Success	Failure
Open-angle	50	31* (62%)	19 (38%)
Narrow-angle	10	2 (20%)	8 (80%)
Secondary	10	5† (50%)	5 (50%)
Total	70	38 (54%)	32 (46%)

* Seventeen patients for over one year.
† Two patients for over one year.

TABLE 2.—*Causes of Failure of Long-Term Acetazoleamide Therapy*
(70 patients)

Diagnosis	No.	Side-Effects	Inadequate Control	Total Failure
Open-angle	50	13 (26%)	6 (12%)	19 (38%)
Narrow-angle	10	4 (40%)	4 (40%)	8 (80%)
Secondary	10	1 (10%)	4 (40%)	5 (50%)
Total	70	18 (26%)	14 (20%)	32 (46%)

Abstracts of the histories of two representative patients in the successfully controlled series are presented.

CASE 1#—M. W. is a 61-year-old white woman with chronic open-angle glaucoma of 12 years' duration. Her glaucoma was controlled at first on miotics, but in recent months had been completely out of control on any miotic therapy. This resulted in rapidly progressing loss of nasal visual field, which threatened the point of fixation in both eyes and led to her admission to McMillan Hospital in March, 1954. In spite of intensive administration of pilocarpine, all intraocular pressures were recorded in the high 40's and low 50's in the right eye and the low 40's in the left eye, with repeated facilities of outflow between 0.02 and 0.06 in both eyes. Treatment was, therefore, started on 250 mg. of acetazoleamide every six hours, in addition to continuation of pilocarpine administration. This resulted in a reduction in intraocular pressure to the range of 18-22 mm. in both eyes without significant change in facilities of outflow. After discharge from the hospital, the patient noted marked anorexia and weight loss for the first two months. The intraocular pressure remained between 22 and 25 mm. in both eyes. She was, therefore, encouraged to continue acetazoleamide, and in May, 1954, the regimen was changed to regular and "delayed action" acetazoleamide (Diamox), 250 mg. of each every 12 hours. Coincident with this change, the patient reported rapid improvement in appetite and gain of weight. Intraocular pressures have remained in the mid-20's up to the present time. Repeated visual fields reveal no further loss during the 13 months of acetazoleamide therapy. There has been no recurrence of anorexia or weight loss.

This patient was referred to the Department by Dr. H. Rommel Hildreth.

CASE 2.—H. R., a 73-year-old Negro with chronic open-angle glaucoma of over five years' duration, persistently refused surgery in spite of progressive loss of vision. Repeated measurements of intraocular pressure in the Clinic were in the high 30's and low to middle 40's in both eyes with markedly decreased facilities of outflow in spite of use of pilocarpine 2% four times daily. Vision, right eye, was reduced to light perception; left eye, 20/70. In a six-month interval, the visual field in the left eye had decreased rapidly, under observation, from upper nasal loss only down to a residual 5 degrees about the point of fixation. Therefore, acetazoleamide, 250 mg. every six hours, was added to his miotic therapy in February, 1954. Since that time, all measurements of intraocular pressure have been in the high teens or low 20's. The facilities of outflow remain at 0.03-0.05 in both eyes. He has experienced only minimal paresthesias. Vision and visual fields remain unchanged after 14 months of acetazoleamide therapy.

C. Chronic Narrow-Angle Glaucoma.—Of the 10 patients with chronic narrow-angle glaucoma subjected to long-term acetazoleamide administration, only 2 met the criteria for successful control (Table 1). The eight failures were equally divided between intolerable side-effects and poor control. Since narrow-angle glaucoma is considered a surgical problem in this Clinic, the 10 patients included in this series are representative of eyes with the poorest prognosis. However, these findings do suggest the inadvisability of relying on acetazoleamide for control of chronic narrow-angle glaucoma.

D. Secondary Glaucoma.—Five of the 10 patients with secondary glaucoma have been controlled successfully (Table 1). Four of the failures in this group were on the basis of poor control of intraocular pressure. This usually resulted from further impairment of the disordered outflow mechanism. Three of the four remain on acetazoleamide in spite of inadequate control because intraocular pressures are maintained at lower levels on acetazoleamide and because further surgery is either refused or considered contraindicated.

E. Ocular Toxicity.—Initially, it was feared that changes might be induced in the lens and other ocular structures by the persistent suppression of aqueous secretion. Repeated careful slit-lamp and ophthalmoscopic examinations have failed to reveal evidence of damage to the lens, retina, or cornea in this series of patients. It should be emphasized that even maximum carbonic anhydrase inhibition in rabbits and man results in only approximately 60% inhibition of aqueous flow.* The residual secretion is apparently adequate in most instances to supply nutrition and carry away waste products for intraocular structures. This contrasts sharply with the not infrequent cataractous changes following some surgical procedures associated with more complete suppression of aqueous flow.

F. Systemic Side-Effects.—Systemic side-effects occurred in 55 patients (79%) of the total series and were severe enough in 18 (26%) to necessitate cessation of acetazoleamide therapy. Side-effects accounted for two-thirds of the failures in open-angle glaucoma (Table 2). Although paresthesias were experienced by almost all patients subjected to acetazoleamide, they were readily tolerated. Potassium chloride administration in doses of 1-2 gm. three times daily was of some help in alleviating this side-effect. Gastrointestinal symptoms, especially anorexia and weight loss, accounted for most of the failures (Table 3). It is important to point out that a number of patients who could be convinced to maintain their weight in spite of anorexia during the first few months of therapy noted spontaneous improvement of appetite, which persisted thereafter (e. g., Case 1). Excessive fatigue was experienced, especially by elderly patients, and in two instances resulted in their stopping therapy. It was necessary for one man to discontinue acetazoleamide because of an exacerbation of ureteral colic, presumably on the basis of alkalization of his urine by the drug.

TABLE 3.—*Side-Effects of Long-Term Acetazoleamide Therapy*
(70 patients)

	Incidence	Severe *
Paresthesias	43 (61%)	0
Gastrointestinal disturbance	34 (49%)	13 (19%)
Excessive fatigue	11 (16%)	2 (3%)
Urinary	3 (4%)	2 (3%)
Hearing loss	2 (3%)	1
Leucopenia	2 (3%)	0
Total	55 (79%)†	18 (26%)

* Necessitating discontinuation of therapy.
† Corrected for multiplicity of symptoms in most patients.

TABLE 4.—*Racial Differences in Causes of Failure of Long-Term Acetazoleamide Therapy*

	No.	Side-Effects	Inadequate Control	Total Failures
White	54	17 (32%)	8 (15%)	25 (47%)
Negro	16	1* (6%)	6 (38%)	7 (44%)
Total	70	18 (26%)	14 (20%)	32 (46%)

* Hearing loss.

Although no racial differences in success rate were noted, the rarity of intolerable side-effects in the 16 Negro patients in this series is worthy of comment (Table 4). The one Negro patient in this series who could not tolerate acetazoleamide experienced the unusual side-effect of severe hearing loss (which proved to be reversible when the drug was stopped).

* Becker, B.: Effects of Diamox on the Composition of the Rabbit Aqueous Humor, presented at the meeting of the Association for Research in Ophthalmology, June 8, 1955. Becker, B.: Evaluation of Glaucoma Therapy by Tonography, presented at the Symposium on Aqueous Flow, International Congress of Ophthalmology, New York, Sept. 21, 1954.

G. Inadequate Control of Intraocular Pressure.—Fourteen patients (20%) in the total series were classified as failures because of inadequate control of intraocular pressure. This was much commoner in the secondary and narrow-angle glaucoma groups. It was associated in most instances with variations in facility of outflow, resulting in pressure rises in spite of persistent partial suppression of secretion. In some patients the addition of ammonium chloride (1-2 gm. every six hours) further lowered the intraocular pressure and permitted adequate control by medical means.

Only six (12%) of the patients with primary open-angle glaucoma could not be maintained in a normotensive state. These six patients have been subjected to careful study in order to learn more about the reasons for acetazoleamide failures. One patient in this group responded well to intramuscular acetazoleamide in spite of failure to respond to oral medication—evidence for poor absorption of acetazoleamide in this particular patient. Two patients demonstrated a progressive decrease of facility of outflow with rising intraocular pressure in spite of effective inhibition of inflow and must be classified as having progression of the basic disease process. The remaining three patients (6% of the open-angle glaucoma series) appeared to be truly resistant to acetazoleamide even at massive dose levels and without alteration in the outflow mechanism. Since all three patients responded well intially, they must be classified as showing "tolerance" to the drug. The nature of this tolerance remains unexplained and is under active investigation.

COMMENT

It is clear from the results in this series that the intraocular pressure of some patients with otherwise uncontrolled chronic glaucoma can be brought under control by the addition of acetazoleamide to their therapeutic regimen. This is in good agreement with the tentative conclusions drawn from a similar study in progress at the Wilmer Institute.[6] Although no significant toxicity has been noted in patients after more than 15 months of therapy, the effects of continuous carbonic anhydrase inhibition over periods of many years still needs elucidation. Therefore, this form of therapy must be considered experimental and can be advocated only in reliable patients who can be carefully followed and observed for possible untoward side-effects, both ocular and systemic. It must be reemphasized that acetazoleamide does not attack the basic disorder of glaucoma, that is, the obstruction to outflow, but is merely a limited means of lowering intraocular pressure by partial suppression of secretion. Therefore, acetazoleamide should not be substituted for measures designed to improve outflow (e. g., miotics or surgery), but merely used as a supplement to such therapy.

Major efforts are needed toward overcoming or avoiding the unpleasant side-effects of acetazoleamide, which occurred in four out of every five patients and which necessitated discontinuing therapy in one out of four patients in this series.

SUMMARY AND CONCLUSIONS

Thirty-one (62%) of 50 patients with open-angle glaucoma uncontrolled by miotics were adequately maintained for periods of 6 to 15 months when around-the-clock acetazoleamide (Diamox) was added to their therapy.

Two-thirds of the open-angle glaucoma failures resulted from intolerable side-effects, most prominent of which was inappetence.

Only six patients (12%) of the 50 in the open-angle glaucoma group responded satisfactorily initially to acetazoleamide but failed to maintain controlled intraocular pressures for over six months. Even more infrequent was the development of true resistance to the drug (6%).

Five of 10 patients with uncontrolled chronic secondary glaucoma were successfully regulated on acetazoleamide.

Only 2 of 10 patients with chronic narrow-angle glaucoma could be satisfactorily maintained on acetazoleamide.

It may be concluded that long-term acetazoleamide administration may be added cautiously to the therapeutic regimen of patients with otherwise uncontrolled glaucoma. However, its use should be restricted to those who can be followed closely and who can be maintained normotensive at tolerated doses of acetazoleamide.

REFERENCES

1. Becker, B.: Decrease in Intraocular Pressure in Man by Carbonic Anhydrase Inhibitor, Diamox, Am. J. Ophth. **37**:13, 1954.

2. Grant, W. M., and Trotter, R. R.: Diamox (Acetazoleamide) in Treatment of Glaucoma, A. M. A. Arch. Ophth. **51**:735, 1954.

3. Breinin, G. M., and Gortz, Heinz: Carbonic Anhydrase Inhibitor Acetazoleamide (Diamox), A. M. A. Arch. Ophth. **52**:333, 1954.

4. Becker, B.: Mechanism of the Fall in Intraocular Pressure Induced by the Carbonic Anhydrase Inhibitor, Diamox, Am. J. Ophth. **39**:177 (Feb., Pt. II) 1955.

5. Green, H.; Capper, S. A.; Bocher, C. A., and Leopold, I. H.: Effect of Acetazoleamide (Diamox) on Carbonic Anhydrase Activity of Anterior Uvea of the Rabbit Eye, A. M. A. Arch. Ophth. **52**:758, 1954.

6. Kupfer, C.; Lawrence, C., and Linner, E.: Long-Term Administration of Acetazoleamide (Diamox) in the Treatment of Glaucoma, to be published.

Artificial Subchoroidal Hemorrhage

Experimental Studies on a New Method of Temporary Shortening of the Inner Coats of the Eye

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Experimental work on Lindner's scleral resection operation * suggested that the following factors play a significant role in bringing about reattachment of the separated retina:

1. The mechanical shortening of the scleral capsule, resulting in a diminution of the volume of the eyeball, so that a shrunken retina can reattach to the sclerochoroidal wall.

2. The inflammation of the choroid and sclera which follows the incisive operation, causing (*a*) a considerable subchoroidal exudation, which fills the suprachoroidal space, and (*b*) a mild subretinal exudation, the result of the inflamed choroid.

The suprachoroidal exudate acts most probably in two ways: mechanically, by further diminishing the choroidal volume, thus bringing the choroid nearer to the detached retina, and by inducing chorioretinal adhesions. The latter is facilitated by the subretinal exudation.

In summary, it was concluded that the mode of action of the scleral resection operation is the correction of a size discrepancy between the retina and the sclerochoroidal wall, combined with an extensive mild inflammation of the choroid.

In evaluating the results of 200 consecutive cases of scleral resection operations for retinal detachment in man, Kronfeld and Pischel [2] came to similar conclusions. These authors attribute the beneficial effect of the operation mainly to correction of the size discrepancy between the retina and the sclerochoroidal capsule; they found that "in cases selected for scleral resection by the criterion of retinal shortage the operation scored 43% successes and 8.5% improvements," a success percentage much higher than is usually expected with this method.

According to these experimental and clinical observations, the shortening of the sclerochoroidal wall seems to be the decisive factor in the success of the scleral resection operation. The suprachoroidal exudation observed in the experimental studies obviously causes a temporary shortening of the choroidal wall only. This suggested the possibility of producing a temporary shortening of the choroidal wall by injecting the individual subject's own blood into the suprachoroidal space.

TECHNIQUE

Twenty-nine normally pigmented eyes from rabbits weighing 8 to 12 lb. (3.6 to 5.4 kg.) were used for the experiments. After general anesthesia with intravenous pentobarbital (Nembutal) sodium, 2 cc. of blood was withdrawn from the artery of the rabbit's ear with a syringe containing 0.2 cc. of 5% sodium citrate as anticoagulant. A retrobulbar injection of 2 cc. of 2% procaine hydrochloride was performed in order to complete the anesthesia and to facilitate luxation of the eye. The luxated eye was held in place by a suture passed through the upper and lower lids near the anterior lid angle, simulating temporary partial tarsorrhaphy. The suture was armed with a small hemostat, care being taken that no pressure was exerted on the eyeball.

Eight millimeters posterior to the limbus a 3-mm.-long equatorial incision was made involving only the exterior half of the sclera, and a mattress nonabsorbable surgical (silk) suture was preplaced through the wound lips. The scleral incision was

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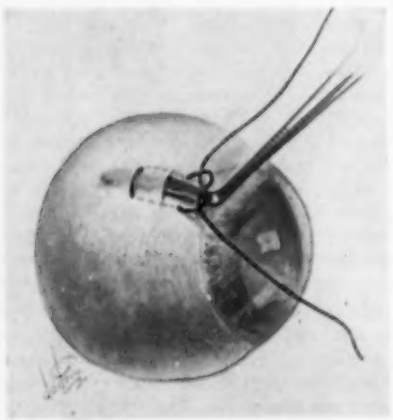
* References 1 and 2.

completed with a small Bard-Parker knife so that an opening of about 1.5 mm. was made, large enough to pass a cyclodialysis spatula. The latter was carefully inserted between sclera and choroid, and the two membranes were separated posterior to the scleral wound for a distance of about 7 mm.; with sideward movements of the spatula the cleft was widened to about 2 or 3 mm.

Reduction of the intraocular pressure was then achieved by one of two methods: (1) anterior chamber puncture, or (2) posterior sclerotomy according to the following method: Opposite the first scleral incision and 8 mm. posterior to the limbus, a 2-mm.-long meridional incision was made involving only the exterior half of the sclera. Through the wound lips a single McLean-type silk suture was preplaced, and the remaining deep scleral layers were opened by a small Bard-Parker knife without injury to the choroid. The choroid was opened by a blunt conical probe or the cyclodialysis spatula. This procedure prevented direct injury of choroidal vessels and subsequent hemorrhage, which might happen if a sharp instrument were used. The vitreous head was repeatedly cut by scissors as it appeared, until the eye became soft. Sometimes, in order to achieve this, gentle pressure on the eyeball with the finger was applied. The preplaced scleral suture was then tightened, closing the sclerotomy wound.

After the eye was softened, the citrated blood was injected between the sclera and the choroid: On the syringe containing the blood a cyclodialysis cannula was inserted and then introduced through a preplaced loose loop of the suture into the preformed suprachoroidal cleft (Fig. 1). The assistant tightened the suture, holding it consistently tight to secure closure of the scleral wound, and blood was injected until the cornea became cloudy. The cyclodialysis spatula was then slowly withdrawn, the suture being still held at tension, so that the wound was immediately closed when the tip of the spatula left the wound lips. This method prevented the injected blood from being expressed by the intraocular pressure. The amount of the injected blood varied from 0.3 to 0.5 cc., depending on the degree of softening of the eye. In some cases with posterior sclerotomy blood leaked under the retina or into the vitreous cavity around the sclerotomy wound. Therefore, the softening of the eye by anterior chamber puncture is more satisfactory than by posterior sclerotomy, though with the first method the eye might not become as soft as desirable in some cases. The surgically treated eyes were enucleated at times varying from several minutes up to 60 days after operation, and the specimens were examined histologically.

Fig. 1.—The cyclodialysis cannula is introduced through a preplaced loop of the suture into the preformed suprachoroidal cleft.



A. OPHTHALMOSCOPIC FINDINGS

Immediately after the operation the whole fundus of albino rabbits tested in preliminary experiments showed a bright red color as a result of the subchoroidal hemorrhage. In normally pigmented eyes the fundus showed a slight degree of red discoloration. Around the site of the injection many small retinal folds were visible immediately after surgery, and in a few eyes in which the amount of injected blood was more than usual a balloon-like protrusion of the choroid and retina was formed. The retinal folds flattened quickly in the following days, so that six to seven days after surgery the fundus had a normal appearance. At the same time, small depigmented choroidal scars, corresponding to the injection wound and the sclerotomy wound, were detectable after careful examination. In cases with posterior sclerotomy small retinal or vitreous hemorrhages were found in the vicinity of the sclerotomy wound.

B. ANATOMICAL FINDINGS

1. *Macroscopic Study.*—After fixation in 10% formalin, the eyes were sectioned on a meridional plane near the injection wound. Examination of the interior of the eye with a magnifying loupe confirmed the ophthalmoscopic findings of the small convoluted retinal folds around the site of the injection, and the small hemorrhages in the vicinity of the sclerotomy wound. The retinal folds

were accompanied in their area by a flat retinal detachment, which disappeared on the sixth to the seventh day after surgery, together with the folds, which in the meantime had gradually flattened out. Between sclera and choroid, a thin, dark-red layer of the injected blood was visible. This blood firmly adhered to the choroid and sclera, so that any attempt to separate the two membranes led to destruction of the choroid.

2. *Microscopic Study*.—Sclera: The histological findings around the scleral wound and the silk thread are essentially the same as those found after similar wounds and are described in detail in previous papers.† Since the wound is very small, only a localized reaction ensues. The scleral wound lips close by connective tissue on the 13th to the 15th day after surgery, leaving a chorioretinal scar at the site of perforation. Occasionally a considerable amount of granulation tissue is found around the silk thread.

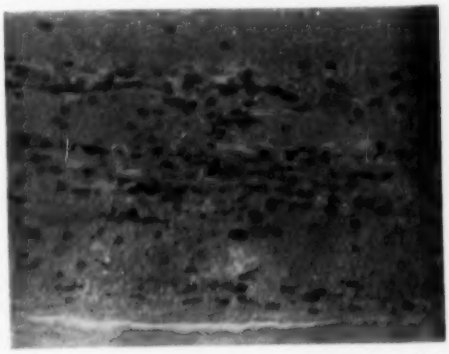
Choroid; Suprachoroidal Space; Ciliary Body: Immediately after the operation the injected blood appears in the suprachoroidal space in a layer 0.15-0.5 mm. thick. Thus, an artificial detachment of the entire choroid and the flat portion of the ciliary body is produced. There are small variations in the thickness of the subchoroidal hemorrhage, which are apparently caused by the normal anatomical connections between the coats of the eye, especially at the scleral spur and the optic disc. The suprachoridea is evenly split by the injected blood into fine pigmented layers, running parallel to the choroid (Fig. 2). The blood itself contains a few leucocytes, which are to be considered as the normal number in the circulating blood.

Several hours after the operation a migration of leucocytes from the choroid, especially the ciliary body, takes place into the injected subchoroidal blood, increasing the leucocytes to five to six times the normal number (Fig. 3). The peak of the leucocytic migration occurs about 24 hours after the operation, but soon thereafter the number of leucocytes decreases rapidly, so that 2 to 3 days after surgery only very few are seen. After the same time interval many young fibroblasts, deriving apparently from the suprachoroidea, appear in the subchoroidal blood (Fig. 5). The pigmented, fine layers of the suprachoroidea appear thinner, or even occasionally interrupted, possibly indicating some disintegrating action of the surrounding blood (Fig. 4). The thickness of the subchoroidal blood is on the whole slightly less than it was one day after the operation, measuring 0.1-0.5 mm.

In the following days the amount of the subchoroidal blood decreases, so that about six to seven days after surgery the blood layer is 0.1-0.25 mm. thick. In the meantime, the fibroblasts in the subchoroidal blood have become more numerous, look flatter, and

Fig. 2 (R#8 L.).—Condition immediately after the injection of the blood (*B*) into the suprachoroidal space; (*S*), sclera. Evenly split suprachoroidea.

Fig. 3 (R#14 R).—Twenty-four hours after surgery. Numerous leucocytes have migrated into the suprachoroidal blood.



† References 1 and 2.

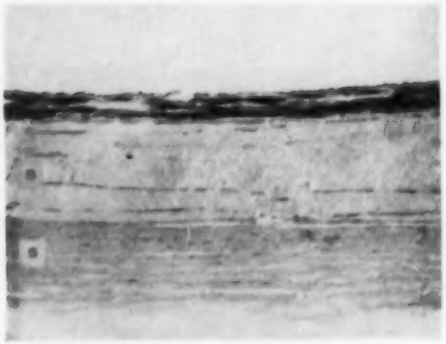
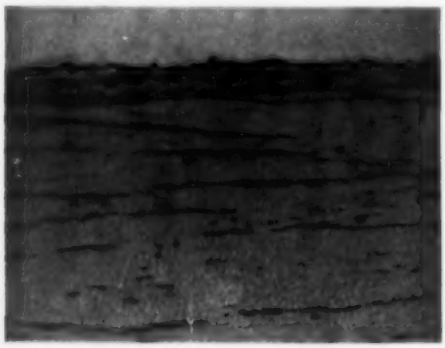


Fig. 4 (R#8 R).—Three days after surgery. Some of the blood has absorbed. Partial disintegration of the suprachoroidal layers. The leucocytes have disappeared. (*B*), blood; (*S*), sclera.

form rows of cells connected with delicate fibers, indicating the beginning of organization (Fig. 6). By that time the leucocytes have entirely disappeared from the blood. There is a decrease in the amount of pigment contained in the blood, and some of it has formed small clusters. The outer layer of the choroid is slightly thickened by increase of the connective tissue cells.

In the next seven days a little more of the subchoroidal blood is absorbed, so that 10 to 13 days after the operation the blood layer is 0.1-0.25 mm. thick and regions adjacent to the ciliary body are often found free of blood. This is possibly due to the higher absorptive action of the ciliary body as compared with that of the choroid, and to the fact that from the beginning the blood layer was relatively

Fig. 5 (R#15 R).—Six days after surgery. Many young fibroblasts in the suprachoroidal blood.



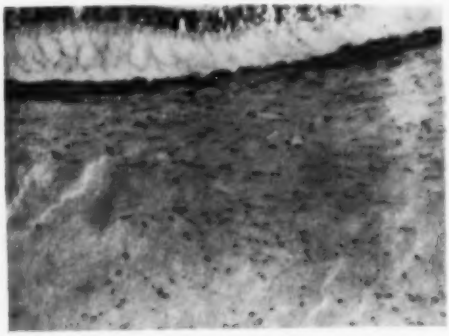


Fig. 6 (R#16 R).—Ten days after surgery. Young connective tissue in the suprachoroidal blood.

thin there. The connective tissue cells in the blood show no appreciable change except that in some instances the formation of more compact tissue has begun. The pigment layers of the suprachoroidea are considerably fewer; pigment appears scattered in small clumps and is sparser than normal, apparently as a result of partial disintegration and subsequent absorption. The choroid shows an increase in the connective tissue cells and an increased density in the outer layers.

Approximately 20 days after the operation the subchoroidal blood has been almost entirely absorbed. Only occasionally (in one out of four cases) a very thin blood layer or scattered red blood cells are visible. Instead, a band of newly formed connective tissue, with numerous nuclei, measuring one to three times the thickness of the average

Fig. 7 (R#19 R).—Twenty days after surgery. *C*, band of young connective tissue between sclera and choroid.

Fig. 8 (R#13 L.).—Thirty days after surgery. Thickening of the choroidal tissue between the large vessels.

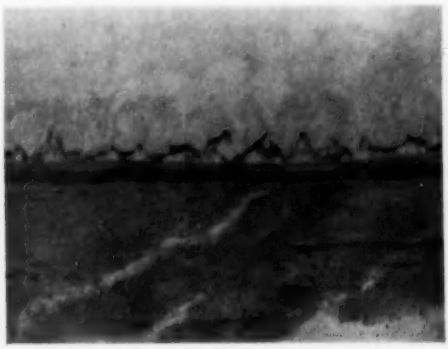
Fig. 10 (R#7 L.).—Sixty days after surgery. No further changes occur in the choroid.

choroid, is visible (Fig. 7). This tissue is thinnest around the optic nerve and near the ciliary body, possibly because in those regions the subchoroidal blood was quickly absorbed. The tissue contains a varying amount of proliferated pigment, depending on the individual rabbit. The connection of this tissue to the inner surface of the sclera is loose; in contrast, it adheres firmly to the outer layers of the choroid, forming in most instances an inseparable unit. This is conclusively shown by the observation that after the histological processing of the specimens the connective tissue is found in many instances separated from the sclera, but very seldom from the choroid. It is obvious that the connective tissue band derives from organization of the subchoroidal blood, that is, from the matured fibroblasts observed in the blood two days after surgery. The thickness of this tissue is considerably less than that of the original blood layer and amounts to only a small fraction of the latter. In some cases, the choroidal tissue itself between the large choroidal vessels, and also the inner layers of the choroid, appear more compact, thicker, and with more nuclei than normal (Fig. 8).

In the subsequent weeks the connective tissue band shows fewer nuclei, becomes slightly thinner and more compact, integrates almost entirely with the outer choroidal layer, and contains an increased amount of proliferated pigment (Fig. 9). This process is completed between the 30th and the 40th day after the operation. The eyes examined

Fig. 9 (R#12 L.).—Thirty-eight days after surgery. Thickened choroid with proliferated pigment. By this time the process of integration of the newly formed connective tissue with the choroid is completed.

Fig. 11 (R#15 R.).—Fringe-like appearance of the pigment epithelium of the retina. On it remains of neuroepithelium are visible.



60 days after surgery show no other changes (Fig. 10).

Retina; Subretinal Space: Because an artificial separation of the retina very often occurs during the histological processing of the specimens, the slides often do not reveal the true relation of the retina to the choroid. Therefore, the following description of the retinal changes is based on the study of both the histological slides and the macroscopic findings of the interior of the eye.

As stated previously, the injected blood spreads quickly in the suprachoroidal space, producing a flat detachment of the entire choroid and ciliary body up to the scleral spur. This causes a shortening of the total surface occupied by the choroid. Owing to its great elasticity, the choroid adapts easily and quickly to the new space conditions by becoming shorter and thicker. The more rigid retina cannot follow the choroid and compensates for the creation of surplus tissue by forming folds and simultaneously detaching itself from the pigment epithelium. Since in the following days the subchoroidal blood absorbs and the choroid resumes its normal size, the retinal folds flatten out and disappear about the sixth to the seventh day after the operation. The retina apparently reattaches anatomically at about the 8th to the 10th day after the operation.

The fine structures of the retina, especially the neuroepithelium, do not show any abnormalities.

About half of the eyes which had an anterior chamber puncture and were examined up to the 10th day after surgery show some albuminous fluid in the subretinal space. This fluid obviously originates from the choroid and represents histologically a transudate.

In the eyes which had a posterior sclerotomy some blood and albuminous fluid is found subretinally up to the 20th day after surgery. The blood derives from the wound of the choroid, absorbs slowly, and disappears three to four weeks after surgery.

Occasionally the pigment epithelium of the retina has a fringe-like appearance, with some of the pigment adhering to the detached neuroepithelium; in rare cases fragments of the neuroepithelium are seen on the pigment epithelium (Fig. 11). These changes are probably caused by the pull which is exerted when the retina suddenly detaches from the choroid.

C. COMPLICATIONS

If the choroid is perforated during the formation of the scleral opening, as happened four times in this series, the operation has to be postponed.

In cases with anterior chamber puncture the iris may prolapse if the intraocular tension rises too much during the subchoroidal blood injection. The iris has to be replaced or, if this is not possible, a peripheral iridectomy has to be performed, as in two cases in these experiments. In cases with posterior sclerotomy it is inevitable that some blood leaks under the retina or into the vitreous. In two cases in this series massive hemorrhage into the vitreous occurred from the sclerotomy wound.

SUMMARY AND CONCLUSIONS

Injection of 03.-05 cc. of the rabbit's own blood into the suprachoroidal space caused (1) flat detachment of the entire uvea for about two weeks, (2) temporary shortening of the choroid, (3) temporary relaxation of the choroidal tissue, and (4) permanent increase in the thickness and compactness of the choroid.

The quick and even distribution of the injected blood in the suprachoroidal space which seems to take place during the injection indicates that the connection between choroid and sclera is very loose in the rabbit eye. The flat detachment of the choroid obviously causes a shortening of the surface occupied by this membrane. The surplus tissue is probably compensated by a thickening of the choroid, and this causes a temporary relaxation of this tissue, evenly distributed over the entire uvea.

The subchoroidal blood is slowly absorbed within three to four weeks. Since the sclera has only few vessels, it is reasonable to assume that the absorption is effected mostly by the choroid. Formation of a fine connec-

tive tissue net within the subchoroidal blood starts two to three days after surgery. This tissue apparently is derived from the cells of the suprachoroidea and becomes slowly denser as the blood gradually absorbs. The connective tissue integrates intimately with the choroid, causing this membrane to become thicker and more compact and to contain an increased amount of pigment.

The temporary formation of the retinal folds in the vicinity of the scleral wound is the result of the creation of surplus tissue through the shortening of the choroid. They soon disappear and seem to have no untoward effects. The absence of histologically visible changes in the retinal structure, especially in the neuroepithelium, shows that neither the blood injection itself nor the secondary changes of the choroid have any damaging effect on the retina.

REFERENCES

1. Dellaporta, A.: Die experimentelle Bulbusverkürzung am Tierauge, von Graefes Arch. Ophth. **152**:28, 1951.

2. Dellaporta, A.: Comparison of Scleral Resection and Scleral Folding in Experimental Shortening of the Eye, A. M. A. Arch. Ophth. **51**:525, 1954.

3. Kronfeld, P. C., and Pischel, D. K.: Scleral Resection Operation for Retinal Detachment, A. M. A. Arch. Ophth. **5**:1:356, 1954.

Electromyography of the Human Extraocular Muscles

I. Normal Kinesiology; Divergence Mechanism

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In the past few years there has been a great deal of interest in the recording of the action potentials of the extraocular muscles. This is a natural extension of the field of clinical electromyography, which has contributed so largely to understanding of the disturbances in nerve and muscle function throughout the body induced by trauma and disease. Studies of the human extraocular muscles were not attempted because of difficulties of technique and instrumentation. These obstacles have been overcome, and we now find ourselves on the threshold of a new understanding of many old problems common to ophthalmology and neurology; indeed, these disciplines are brought into even closer harmony.

HISTORY

High lights in the evolution of electrophysiologic concepts of nerve and muscle function are the following: 1. Dubois-Reymond, in 1848,[1] established the "action current" principle, or wave of electrical negativity of the nerve impulse. 2. Piper,[2] in 1907, obtained the first recorded electromyogram. 3. Erlanger and Gasser, in 1926[3] and 1937,[4] with others, described the use of the cathode ray oscilloscope for nerve-impulse recording. 4. Adrian and Bronk,[5] in 1929, introduced concentric needle electrodes. 5. Denny-Brown and Pennybacker,[6] in 1938, analyzed fibrillation potentials in denervated muscles.

Outstanding with respect to the extraocular muscles were the classic works of Sherrington on reciprocal innervation and Hering on the equal distribution of nerve impulses between contralateral synergists. Other important works were the electrical studies of Cooper and Eccles,[7] 1930; Lorente de Nó,[8] 1935; Brown and Harvey,[9] 1941; Reid,[10] 1949; Pulfrich,[11] 1952; Adler,[12] 1953, and Magee,[13] 1954. The outstanding papers of Björk and Kugelberg (1952-1954)* deserve special mention. These workers have presented the first detailed study of electromyography of extraocular muscles in man. Our techniques differ chiefly in that we have mostly used the coaxial electrode rather than the monopolar electrode.

The study of the action potentials of the extraocular muscles in man is of tremendous importance for several reasons. It affords a unique insight into the innervational factors of normal eye muscle activity and is thus of basic physiologic interest. It provides a tool for analysis of altered or impaired ocular motility on the clinical level and is thus of great practical interest. Our own studies and those of Björk and Kugelberg clearly indicate the potentialities for ophthalmologic and neurologic diagnosis inherent

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* References 14 through 18.

in this approach. We feel that a more complete understanding of many clinical motility entities is at hand.

In a series of papers, we shall present electromyographic data on the following topics:

1. Kinesiology of the extraocular muscles
2. Paretic strabismus; ptosis
3. Nystagmus
4. Supranuclear mechanisms
5. Comitant strabismus
6. Myopathies and neuropathies

The present paper is a preliminary report dealing with normal kinesiology. The nature of the divergence mechanism in a patient with intermittent exotropia will also be described.

MATERIALS AND METHODS

Critical electrophysiologic work requires high standards of instrumentation. We employ a dual-beam cathode-ray oscilloscope with a high-grain preamplifier and audioamplifier. Recordings are made by photography with a variable-speed 35 mm. moving film camera. Tape recording for sound is also available. A second oscilloscope is used as a monitor. A time signal can be fed into one channel while the other records the muscle potential. Both beams are used to record simultaneously from two muscles. Time markers of 1000 and 100 cycles and camera speeds of 10 cm/sec., 25 cm/sec., and sometimes 50 cm/sec. are used. Traces can be suitably displayed by increasing either the sweep speed or the film speed. A well-shielded room which provides an almost noiseless isoelectric base line is *sine qua non*.

A concentric needle electrode made from a 27-gauge needle is inserted into the muscle. We prefer this to the monopolar electrode, since it seems to be more selective in pick-up, and thus less subject to criticism of recording extraneous or distant potentials. It also affords greater detail for analysis of the motor units. Larger-gauge electrodes produce excessive trauma, with frequent subconjunctival hemorrhages. This is minimized with the present electrode, and subsequent discomfort or reaction is slight. Care must be exercised to prevent exposure keratitis—drops of 1% methylcellulose suffice to maintain corneal moisture. Topical anesthesia is adequate for all needle insertions through the conjunctiva. The orbicularis oculi requires a skin approach after procaine anesthesia. A blepharostat is necessary for placement of the electrodes. Insertion of the sterile needle into the rectus muscles is made through the conjunctiva anterior to the tendon insertion and thence into the muscle belly (Fig. 1). In this way the conjunctiva helps to stabilize the electrode. A burst of impulses records proper placement. A ground electrode is affixed to the patient's forehead. Deviations and displacements of the eyes are measured on a hand perimeter.

ELECTROMYOGRAPHIC PRINCIPLES

The technical details of electromyography are unfamiliar to most ophthalmologists; hence a brief exposition is warranted. The nerve impulse is generated in the cell body of the neuron and distributed through the axon and all its subdivisions to the muscle cells it innervates. The cell body, axon, and muscle cells in this series constitute the motor unit. The electrode picks up the integrated voltage of the synchronous discharge of the muscle cells of the unit. This appears on the oscilloscope as an electrical wave form of diphasic or triphasic character when the needle is properly placed. A monophasic, i. e., a negative or positive, wave may result from asymmetric positioning of the electrode. Polyphasic potentials are occasionally found in normal skeletal muscles, but rarely occur in the extraocular muscles. The effect of the body as a volume conductor may alter the wave form, and frequently an envelope pattern occurs, which can be resolved into its component potentials by suitable electrode positioning.

The anatomical motor unit in the extraocular muscles is very much smaller than that of skeletal muscle. The innervation ratio of the soleus is said to be 1 nerve fiber to 100-150 muscle fibers (Clark,[19] 1931), whereas that of the extraocular muscles consists of 1 nerve fiber to only 5-10 muscle fibers (Tergast,[20] 1873).

This difference finds expression in the configuration of the electrical motor unit, or action potential, which is often complex in skeletal muscle and usually simple in extraocular muscle. Under pathologic conditions slightly asynchronous discharge of the motor unit results in a "polyphasic" potential.

In general, a low innervation ratio is characteristic of muscles involved in delicate, precise, and complex movements, such as the eye muscles and small muscles of the

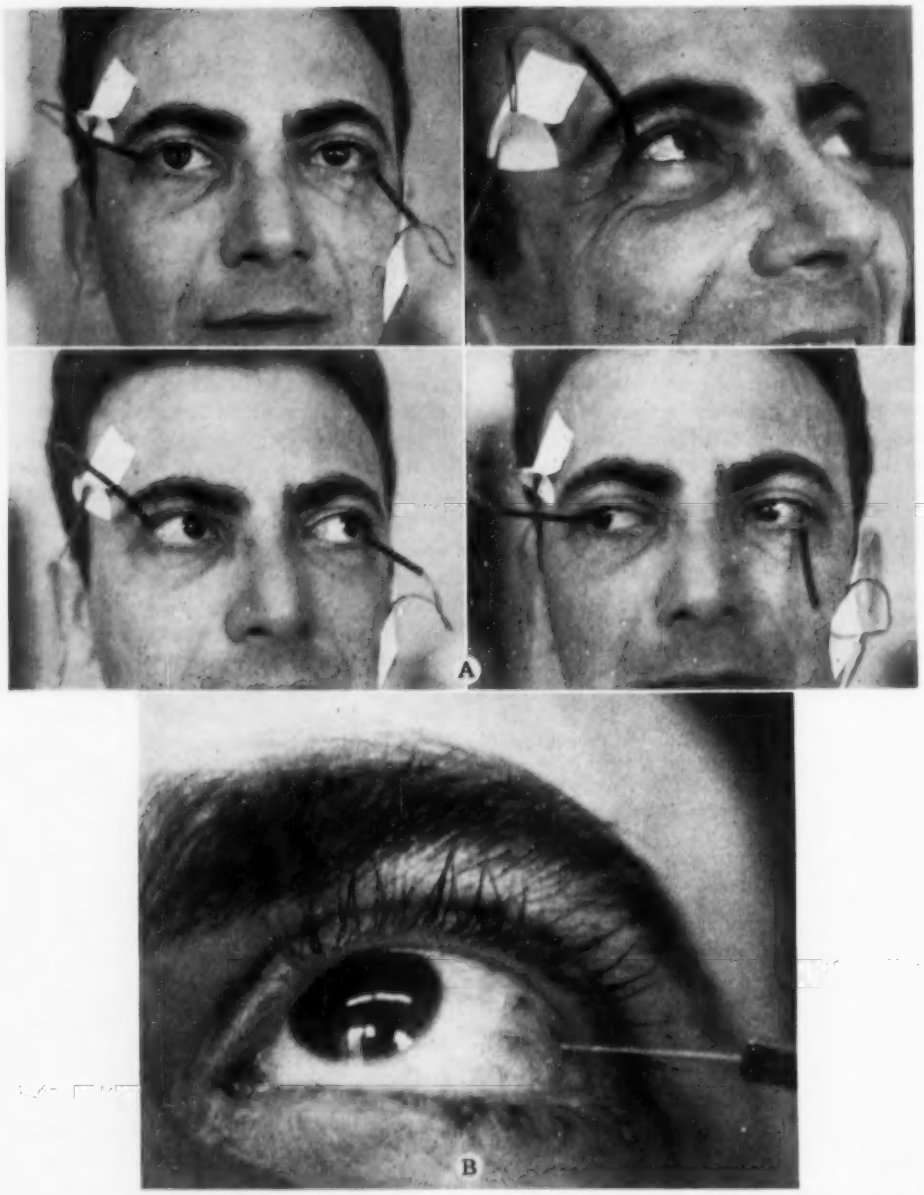

Fig. 1.—*A*, patient with electrodes inserted in lateral recti. Discomfort and reaction are slight. *B*, close-up of inserted electrode.

hands, whereas a large ratio is characteristic of muscles used for gross actions, such as those of the limbs and trunk.

Skeletal muscle at rest evinces no potential recordable with present-day instruments. As will be seen, this is not true of the extraocular muscles, which rarely are electrically silent. A skeletal muscle responds to an increased innervation in several ways. The frequency of discharge of the motor unit

increases, and additional units are recruited, which may be of much larger amplitude. Thus, the pattern of activity goes from resting silence to a few units on minimal effort to a thunderous barrage of firing units on maximum effort. The last state does not permit analysis of individual units, owing to their great number and density. On the audioamplifier the sound changes from a pop or crackle of individual units to the crashing obbligato of profuse firing. It is sometimes easier to hear than to see a unit. Average normal values for skeletal motor units are as follows: amplitude, 100-3000 μv; duration, 5-10 msec.; frequency, 5-30/sec. An oscilloscope with suitable preamplification is essential to display the traces of such small, fast potentials.

Characteristic alterations of the electrical activity have been described in lower motor neuron lesions, myopathies, and other neurologic conditions. A most useful diagnostic finding is the fibrillation potential of denervation. These potentials are considered the output of an individual muscle fiber and show an amplitude of 5-100 μv, a duration of 1-2 msec., and a frequency of 5-30/sec. In man they develop about two to three weeks after denervation. They occur while the muscle is at rest. When denervation is complete, no volitional potentials are obtainable. In partial denervation a combination of fibrillation with volitional potentials is found. If recovery occurs, there is a gradual development of "polyphasic" potentials, which, in turn, give place to normal motor units. A certain number of fibrillations and "polyphasics" may persist up to and after complete clinical recovery. Other abnormal potentials may also appear: Positive slow-wave potentials of 5-10 msec. are also seen in denervation with insertion of the electrodes.

Paralysis resulting from compression of a nerve without denervation results in electrical silence at rest and on volition.

Upper motor neuron lesions may reveal simultaneous activity of antagonists, synchrony of firing, and disturbances of reciprocity.

Muscular dystrophy exhibits low amplitude of motor units due to progressive destruction of muscle fibers.

CLINICAL MATERIAL

We have utilized normal volunteers for studies in kinesiology and nystagmus. All have had good vision in both eyes and, despite binocular application of electrodes, have had no ill effects. Some corneal exposure and subconjunctival hemorrhages occurred in several subjects prior to the use of the fine electrode. Since then, discomfort has been minimal and the method appears eminently practical, particularly since non-kinesiologic studies require very little time. Several volunteers had fine electrodes inserted for periods of one to two hours without pain or difficulty.

OBSERVATIONS

A. Action Potentials.—The extraocular muscles show a basic similarity in their motor units. The following characteristics are listed by Björk[14]: average amplitude, 20-150 μv; duration, 1-2 msec., and frequency, up to 150 per second. Although these figures agree well with our material with respect to the duration, we hesitate to give figures on amplitude or frequency because these factors vary so greatly with electrode position and effort. The importance of electrode position cannot be overemphasized. A slight variation may cause an increase in amplitude of hundreds of microvolts. We have recorded amplitudes of 400-600 μv in some muscles. A muscle must be sampled at several points before conclusions as to function may be drawn. A striking characteristic of extraocular muscles is the presence of marked activity in the primary position. Even in versions the firing of inhibited muscle does not fall off to zero except in the most extreme movement out of the muscle field. In this the extraocular muscle is in contrast to skeletal muscle, which is electrically silent at rest. There is, in fact, no position of rest for extraocular muscles. When the eye is moved into the field of action, the frequency of firing in-

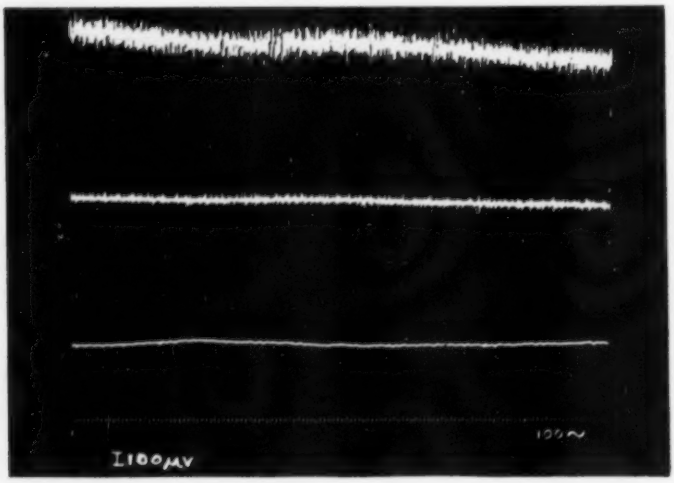

Fig. 2.—Lateral rectus, O.D.

Upper tracing records field of maximum activity (abduction); middle tracing, primary position with rhythmic motor unit activity; lower tracing, inhibition in the adducted position. Time in 100 cycles.

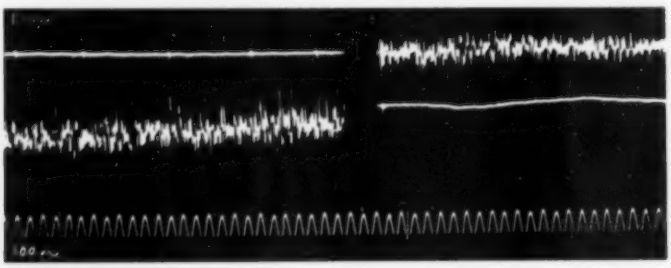

Fig. 3.—Reciprocal relationship. Lateral recti of the two eyes: upper tracing, O.D.; lower tracing, O.S.

On extreme gaze right there is marked activity of the lateral rectus O.D. with almost complete inhibition of the left lateral rectus.

On extreme gaze left the left lateral rectus fires maximally, while there is complete inhibition of the right lateral rectus.

creases, new units are recruited, and increased amplitude is seen (Fig. 2). We see a graded increase of activity in the agonist on versions and a simultaneous graded decrease of activity of the antagonist (Fig. 3). Sherrington's law of reciprocal relations is thus beautifully exemplified in the direct and contralateral antagonists. Synergists show a parallel increase of activity.

Figure 4 illustrates the firing of the medial rectus in adduction with excellent needle position. The amplitude is large (400 μv). The lower tracing shows the individual units spread out by fast camera speed (50 cm/sec.).

B. Convergence Potentials.—Convergence is characterized by increasing amplitude, frequency, and recruitment in the medial recti (Fig. 5*A*), whereas the lateral recti are increasingly inhibited. Slight activity of the lateral rectus, however, persists until the break, when the convergence near point is exceeded. Just prior to the break, on deviation of the gaze to the side away from its field, the slight activity of the lateral rectus falls off to zero. Fusional prism conver-

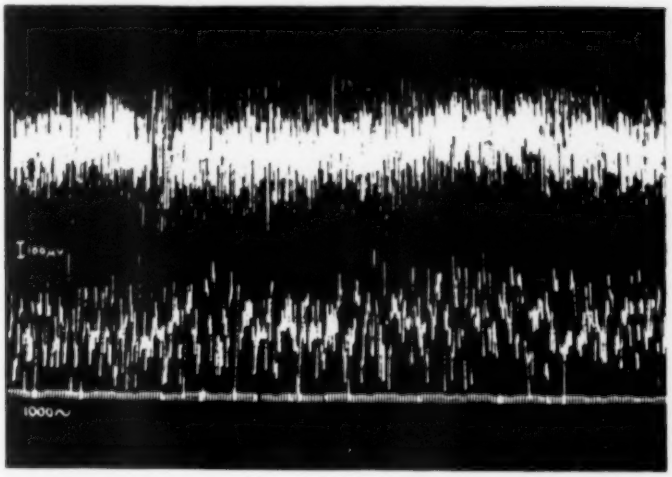

Fig. 4.—Medial rectus of right eye.
Upper tracing records large activity in adduction at 10 cm/sec.; lower tracing, same muscle at fast camera speed of 50 cm/sec.

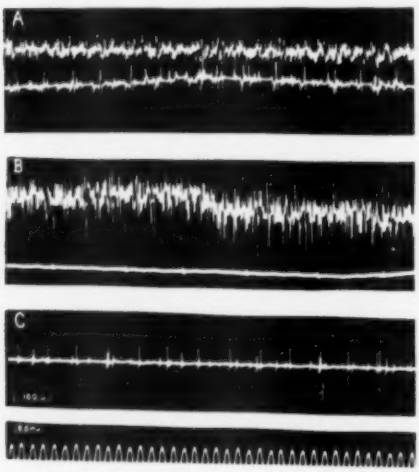

Fig. 5.—Both medial recti recorded: upper record, O.S.; lower record, O.D.
A, convergence. slightly less activity is recorded in right eye. A few individual large units can be identified.
B, dextroversion. There is marked increase of activity with larger amplitude in the left medial rectus, while the right medial rectus is inhibited except for an occasional remote unit.
C, right medial rectus alone with examples of single units.

gence is accompanied by the same recruitment. The motor units are not as large as those seen when the muscle fires maximally in a version (Fig. 5*B*).

C. Divergence Potentials. — Divergence presents a particularly interesting problem, inasmuch as the ancient controversy over the existence of an active or a passive divergence mechanism, with the related question as to existence of a divergence center, still rages. Recent work by Adler[12] (1953) with a kymographic method indicated that active innervation of a lateral rectus occurred in a normal subject during divergence. With the great sensitivity and freedom from inertia of our equipment, we have been able to analyze the divergence function in an instructive subject—a patient with intermittent exotropia. This case merits a special account, since it conclusively demonstrates that divergence is definitely associated with active innervation of the lateral recti. The concept of divergence based solely on the inhibition of convergence and elasticity of the orbital tissues, fascia, and muscles cannot be countenanced any longer.

J. R., a 31-year-old white man, had a 15-year history of intermittent divergence of the left eye. This had increased in frequency and amount through the years, although he retained the ability to fuse on effort. He also maintained a close N. P. C., although on near fixation the left eye turned out frequently. He presented a "swinging-gate" phenomenon with divergence of the left eye up to 45 degrees. Prism measurements showed exo deviation

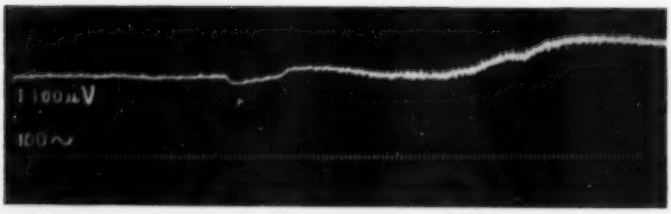

Fig. 6a.—Intermittent exotropia with remote fixation. Lateral rectus of diverging eye shows marked increase of firing as eye breaks from fusion into exotropia.

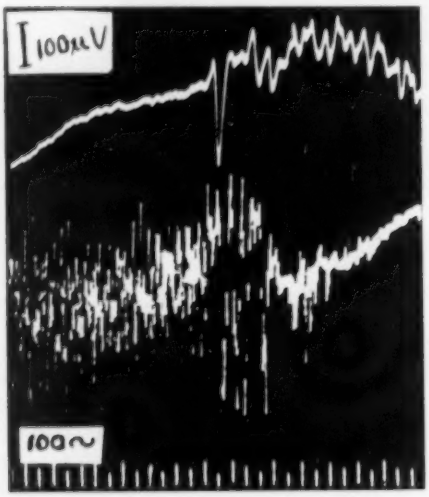

Fig. 6.—Divergence in intermittent exotropia. Lateral rectus above; medial rectus below.

On convergence the activity of the medial rectus increases, while the lateral rectus is increasingly inhibited. At the break there is marked activity in the lateral rectus, which overlaps continued activity in the medial rectus for 20 msec., after which inhibition of the medial rectus occurs. The firing in the lateral rectus persists so long as the eye remains divergent.

of 70△ for distance and near. Vision was 20/20 in each eye, and the refractive error was a small hyperopia.

Electrodes were inserted in the left medial and lateral rectus muscles. Activity of both muscles was good. As soon as divergence occurred, the activity of the lateral rectus increased markedly while the medial rectus was inhibited. This phenomenon occurred at all times when the left eye turned out. On reestablishment of fusion the reverse took place.

These data are subject to the criticism that the patient was fixing a point only 3 to 4 meters distant in the room, and hence it may be argued that convergence influence was present. That this could vitiate the result seems quite unlikely; furthermore, the phenomenon was the same no matter how fusion was broken, and even when the eyes were covered. The lateral rectus fired maximally whenever the eye turned out. On determining the divergence break after convergence, a most instructive tracing was obtained (Fig. 6). The medial rectus firing increased in amplitude and frequency on convergence, while the activity of the lateral rectus decreased. However, just before the eye diverged the inhibited lateral rectus fired large potentials for a period of 20 msec., during which time the medial rectus was still increasing its discharge. Then inhibition of the medial rectus occurred and the eye diverged, while marked firing continued in the lateral rectus. Not only was divergence associated with increased activity in the lateral rectus but this increase occurred prior to the inhibition of the medial rectus—pulling, as it were, against it. The activity in the lateral rectus continued as long as the eye remained divergent and paralleled that which accompanied divergence at other distances. This apparent negation of Sherrington's law suggests that divergence is indeed an independent function and may be a manifestation of a fundamental disturbance in intermittent exotropia. No such disturbance in reciprocity occurs in the rapid movements of nystagmus. The source of divergence activity thus manifested remains unknown. It lends impetus to the search for a divergence center and will probably gratify the proponents of the divergence excess concept of intermittent exotropia.

Fusional prism divergence did not seem to increase the activity of lateral rectus firing, perhaps because fusional divergence

amplitudes in the normals studied were so very low, especially after bilateral electrode insertions, not exceeding a few diopters.

A second case of long-standing intermittent exotropia has been studied electromyographically.

D. S., a 29-year-old white man, has had alternating intermittent divergence since childhood. Originally present at distance only, it has increased in degree until the present, when his eyes are divergent most of the time. With effort, he fuses at both distant and near fixation points. The N.P.C. is close. Prism measurements showed exo deviation of 70△ for both distance and near. A small myopic refractive error was corrected to 20/20 O. U. Electrodes were inserted in the medial and lateral recti of the right eye.

Whenever the eye diverged, there was a marked increase of activity in the lateral rectus. This was true for all distances of fixation. When the patient was asked to observe a fixation point at about ¼ mile distance, he could briefly maintain fusion with effort but lapsed into a divergence of 70△. At the onset of divergence, the firing of the lateral rectus increased, reaching a maximum in the most divergent position and maintaining this level so long as the eye remained divergent. This degree of activity was the equal of that seen in extreme lateral version to that side. There is no possibility of convergence playing a role under such circumstances. This case completely bears out the findings of the previous case of intermittent exotropia and establishes beyond question that divergence is associated with active innervation of the lateral rectus (Fig. 6a).

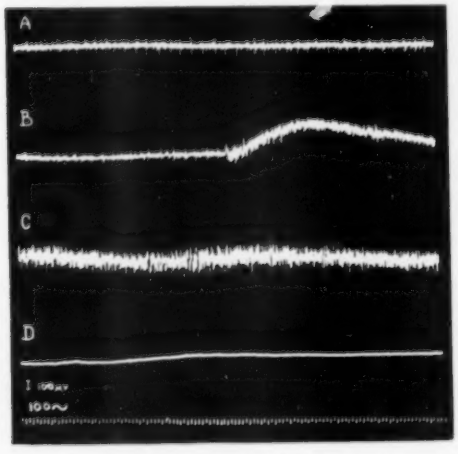

Fig. 7.—Field of action of left inferior oblique.

A, primary position. Note rhythmic firing of single motor units intermingled with other electrical activity.

B, movement from primary position to up and in and then up and out. Initial activity with single motor units bursts into large activity as the eye goes into nasal field of elevation; activity is slightly less in the temporal field of elevation.

C, maximum field of activity with sustained firing.

D, inhibition of activity on downward gaze.

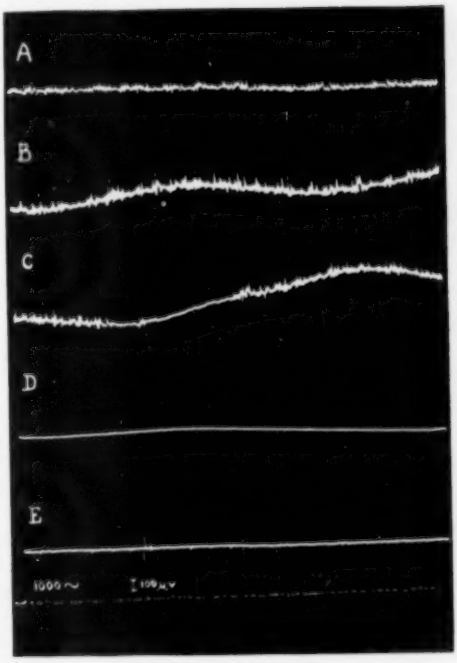

Fig. 8.—Levator palpebrae superioris.

A, primary position. Moderate sustained activity is present.

B, upward gaze. Increased firing occurs.

C, blinking due to corneal reflex seen as inhibition in middle third.

D, downward gaze. No activity is present.

E, a single motor unit recorded in the same muscle.

D. Fields of Action.—The horizontal recti are active in the primary position. On gaze up and gaze down the activity remains at about the same level, although occasionally it appears to increase slightly. The field of the inferior oblique is instructive (Fig. 7). The muscle firing is greatest in the superior nasal field, where maximum elevation occurs. The muscle activity is slightly less in the superior temporal field, where torsional function is maximum. In the primary position it

is moderate in amount but falls to zero below the horizontal plane.

E. Levator Palpebrae.—Insertion of the electrode through the upper fornix is easily accomplished by everting the lid over a Desmarres retractor. The action potentials are brisk, increasing greatly on upward gaze (Fig. 8). The activity decreases to a minimum or zero on extreme downward gaze. Well-developed reciprocity existing between the levator and the orbicularis is clearly shown in blinks, as was reported by Björk and Kugelberg.[16] In our series there does not seem to be any significant difference between the action potential of the levator and that of the recti muscles, such as was suggested by these authors.[15] Electromyography is important in studies of ptosis. For example, a patient with complete third nerve palsy of three months' duration due to a proved aneurysm showed a characteristic train of fibrillation potentials of denervation while at rest, which persisted throughout the period of examination. No voluntary potentials whatever could be elicited. This case will be reported subsequently with other examples of paralysis. The levator lends itself to the demonstration of altered innervation of myasthenia gravis and the response to drugs.

F. Orbicularis Oculi.—The activity of this muscle appears intermediate between the extraocular and the skeletal muscles. On forced closure of the lids the amplitude becomes tremendous, and recruitment and frequency increase greatly (Fig. 9). The motor units often exhibit the simpler pattern of the extraocular muscles. The corneal blink reflex can readily be shown as a rapid augmentation of discharge with concomitant inhibition of the levator (Fig. 8). In a patient with myotonia atrophica the orbicularis showed no voluntary potentials. The lack of muscular structure was confirmed by electrical stimulation studies. Closure of the eyes was effected solely by levator inhibition.

G. Reliability of Tracings.—We have been struck with the consistency and reproducibility of EMG patterns, despite the fact that the needle must undergo slight changes of position in movement. In one patient a single motor unit fired steadily in the same eye position for an hour without altering form or frequency, despite various movements during that time. On the eye returning to the same position, the activity was identical, indicating fixity of the electrode-unit relationship.

When the globe was fixed immovably with forceps, the innervation pattern on attempted movement corresponded with that of the freely rotating globe; so it is the effort of innervation that determines the rate, amplitude, and recruitment of units. Augmentation of the agonist and inhibition of the antagonist occur just as though the globe were free to follow the muscle pull. These findings

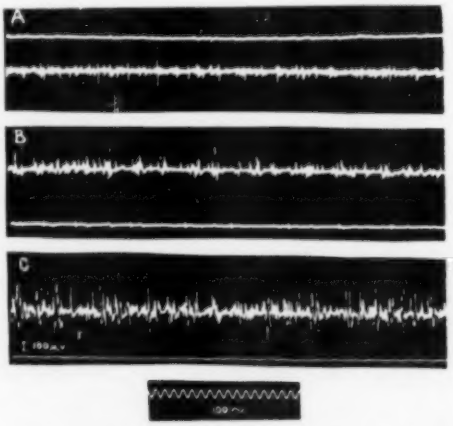

Fig. 9.—Orbicularis oculi and levator palpebrae superioris simultaneously recorded (orbicularis above; levator below).

(*A*) On upward gaze the levator is active, while the orbicularis is inhibited.

(*B*) On closure of the eye the orbicularis fires, while the levator is inhibited except for a single unit discharge.

(*C*) On forced closure there is marked increase of orbicularis activity and total inhibition of the levator.

were reported by Björk[15] and have been completely confirmed by us. Passive movement of the globe does not produce or alter the activity, which always accords with the volitional effort. Covering the eyes makes no difference—the level of activity is independent of the visual act. Fixation serves as the guide to bring the eye to bear on a particular object of interest. The same level

of activity develops whenever the globe describes the requisite rotation to arrive at that point—seeing or not seeing—because it takes the same amount of energy to accomplish the movement. This has a bearing upon the significance of the fixing eye in strabismus and the prism measurement of deviations, as will be described subsequently.

H. Paretic Strabismus.—Extraocular muscle palsies investigated electromyographically will be reported later. Definite fibrillation, indicating denervation, can be shown in some cases. It should be possible to differentiate a pressure paralysis with a block of conduction from denervating lesions by the presence of electrical silence in the former and fibrillations in the latter. The importance of such studies is self-evident—we should be able to anticipate early functional recovery in the former and a poor prognosis in the latter. A primary muscular atrophy could be distinguishable from a neural atrophy by the pattern of the EMG.

I. Comitant Strabismus.—This will also be reported on subsequently. It is unfortunate that this method cannot be used readily in children because of the necessity for general anesthesia. We plan to study muscle activity at the operative table during the induction of anesthesia, and with direct insertion of electrodes in the exposed muscle.

J. Nystagmus.—No finer method exists for recording nystagmus potentials in the human than electromyography. Spontaneous and induced nystagmus potentials have been recorded. Optokinetic and vestibular nystagmus are readily elicited, the latter by means of cold water in the external auditory canal. We have been astounded by the beautiful tracings of extremely rapid rates of caloric nystagmus that are displayed in detail even at durations of 30 msec. or less (Fig. 10). There is perfect reciprocity in the normal. Studies on pathologic nystagmus are in progress.

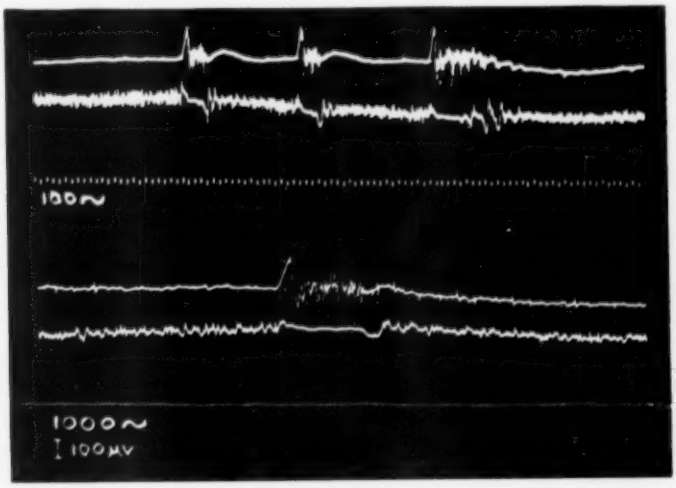

Fig. 10.—Caloric nystagmus (cold water in right ear). Upper, left lateral rectus; lower, right lateral rectus. Time, 100 cycles.

In upper tracings occur extremely rapid nystagmus episodes. Note reciprocal relationship between these contralateral antagonists. Base line showed absence of activity in the left lateral rectus, while fair activity was present in the right lateral rectus, owing to gaze being directed to the right. A sudden burst of marked activity in the left lateral rectus corresponded to complete silence of the right lateral rectus.

One nystagmus episode is recorded from the same muscle at fast speed. Time 1000 cycles.

SUMMARY

Electromyography of the extraocular muscles in man is clinically feasible, relatively simple, and without ill effects. It provides an important tool for physiologic studies of

innervational factors affecting the extraocular muscles. It may prove to be a new and significant aid to clinical diagnosis and prognosis—a matter of great interest to the neurologist, as well as the ophthalmologist.

Electromyograms are presented showing the character of the action currents in the extraocular muscles. The motor unit is simpler than in skeletal muscle, is of shorter duration, and can fire at greater frequency.

There is no position of innervational rest. The muscles actively fire in the primary position and at all times except in extreme movements out of their field. Reciprocal innervation in versions, vergences, and lid movements is exhibited by graded decrementation of the antagonist with augmentation of the agonist in the same and the opposite eye. This relationship can be very rapid. The field of action of a muscle is readily demonstrated.

Spontaneous, optokinetic, and vestibular nystagmus potentials are recorded in sharp, clear-cut patterns. Caloric nystagmus, as fast as 30 msec. or less, is displayed in detail. Electromyography provides the finest demonstration of these phenomena obtainable.

Paretic muscle involvements can be analyzed by the EMG, subject to certain limitations. Fibrillation potentials have been obtained in denervating lesions.

Cases of intermittent exotropia are described in which active divergence innervation to the lateral rectus occurred. Divergence cannot be considered a passive phenomenon, but the source of divergence activity remains to be discovered.

REFERENCES

1. DuBois-Reymond, E.: Untersuchungen über thierische Elektricität, Berlin, G. Reimer, 1848.

2. Piper, H.: Über den willkürlicher Muskeltetanus, Arch. ges. Physiol. **119**:301, 1907.

3. Erlanger, J.: Analysis of Action Potential of Nerve, Harvey Lect. **22**:90, 1926.

4. Erlanger, J., and Gasser, W.: Electrical Signs of Nervous Activity, Philadelphia, University of Pennsylvania Press, 1937.

5. Adrian, E. D., and Bronk, D. W.: Frequency of Discharge in Reflex and Voluntary Contractions, J. Physiol. **67**:119, 1929.

6. Denny-Brown, D., and Pennybacker, J.: Fibrillation and Fasciculation in Voluntary Muscle, Brain **61**:311, 1938.

7. Cooper, S., and Eccles, J. C.: The Isometric Responses of Mammalian Muscles, J. Physiol. **69**:377, 1930.

8. Lorente de Nó, R.: The Effect of an Antidromic Impulse on the Response of the Motoneurone, Am. J. Physiol. **112**:595, 1935.

9. Brown, G. L., and Harvey, A. M.: Neuro-Muscular Transmission in the Extrinsic Muscles of the Eye, J. Physiol. **99**:379, 1941.

10. Reid, G.: The Rate of Discharge of the Extraocular Motoneurones, J. Physiol. **110**:217, 1949.

11. Pulfrich, K.: Aktionsströme äusserer Augenmuskeln, von Graefes Arch. Ophth. **152**:731, 1952.

12. Adler, F. H.: Pathologic Physiology of Strabismus, A. M. A. Arch. Ophth. **50**:19, 1953.

13. Magee, A. J.: Electromyogram of the Extraocular Muscles of the Rabbit in Situ, A. M. A. Arch. Ophth. **52**:212, 1954.

14. Björk, A.: Electrical Activity of Human Extrinsic Eye Muscles, Experientia **8**:226, 1952.

15. Björk, A., and Kugelberg, E.: Motor Unit Activity in the Human Extraocular Muscles, Electroencephalog. & Clin. Neurophysiol. **5**:271, 1953.

16. Björk, A., and Kugelberg, E.: The Electrical Activity of the Muscles of the Eye and Eyelids in Various Positions and During Movement, Electroencephalog. & Clin. Neurophysiol. **5**:595, 1953.

17. Björk, A.: Electromyographic Study of Conditions Involving Limited Mobility of the Eye Chiefly Due to Neurogenic Pareses, Brit. J. Ophth. **38**:528, 1954.

18. Björk, A.: Electromyographic Studies on the Coordination of Antagonistic Muscles in Cases of Abducens and Facial Palsy, Brit. J. Ophth. **38**:605, 1954.

19. Clark, D. A.: Muscle Counts of Motor Units: A Study in Innervation Ratios, Am. J. Physiol. **96**:296, 1931.

20. Tergast, P.: Über das Verhältniss von Nerve und Muskel, Arch. mikr. Anat. **9**:36-46, 1873.

Additional References

Denny-Brown, D.: Interpretation of the Electromyogram, Arch. Neurol. & Psychiat. **61**:99, 1949.

Hoefer, P., and Putnam, T.: Electromyographic Studies of Normal and Abnormal Movement, Tr. Am. Neurol. A. **65**:18, 1939.

Jasper, H. H., and Ballen, G.: Unipolar Electromyograms of Normal and Denervated Human Muscle, J. Neurophysiol. **12**:231, 1949.

Weddell, G.; Feinstein, B., and Pattle, R. E.: Clinical Application of Electromyography, Lancet **1**:236, 1943.

Conjunctivitis in Adenoidal-Pharyngeal-Conjunctival Virus Infection

Pharyngoconjunctival Fever, a Newly Described Entity

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Conjunctivitis is an entity often taken lightly by both the physician and the public. Many causative agents are known, and effective therapy is found for most of them. However, cases are still sometimes seen which not only appear resistant to commonly prescribed therapeutic measures but may have the additional danger that they are caused by easily transmissible pathogenic agents, leading to epidemic outbreaks. Such types of conjunctivitis may be responsible for considerable morbidity and loss of time from schools, offices, and factories. Virus agents are notably difficult to isolate and identify, and only a few are known to respond to present antibiotic and chemotherapeutic agents.

In recent years references have been made to conjunctivitis appearing in epidemic form with characteristics suggestive of a viral origin but not fitting into classifications of known virus conjunctivitides. Association with swimming pools or dissemination attributed to ophthalmologists' instruments have in the past been linked with entities which were not as clearly defined as could be desired.* One might surmise that this confusion has been increased in some instances by two or more viral agents being involved in the same epidemic outbreak. Further difficulties may have been introduced by pathogenic viruses undergoing mutation or changes in characteristics from one outbreak to another.

It should not be surprising to ophthalmologists and otolaryngologists, therefore, that since early in 1954 a new disease entity, pharyngoconjunctival fever, has been described and added to the previously known virus diseases associated with conjunctivitis and nasopharyngitis. The causative agent has been identified as Type 3 of a group of viruses called "APC" (adenoidal-pharyngeal-conjunctival) viruses because of the sites from which members of the group were first isolated. Others of the APC viruses have not been definitely implicated as spontaneously causing conjunctivitis, though their importance in the field of respiratory disease appears considerable.

OBSERVATIONS ON FIRST RECOGNIZED CASES

Description of the first few cases from which Type 3 APC virus was recovered largely sets the pattern of observed ocular findings in pharyngoconjunctival fever. In early February, 1954, a laboratory technician exposed to Type 3 APC virus developed uniocular conjunctivitis without demonstrable fever or other evidence of systemic

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National Institutes of Health, Department of Health, Education, and Welfare, U. S. Public Health Service. Acting Chief, Ophthalmology Branch, National Institute of Neurological Diseases and Blindness (Dr. Ryan). Ophthalmology Branch, National Institute of Neurological Diseases and Blindness (Drs. O'Rourke and Iser).

* References 4 and 5.

disease except slight soreness and injection of the throat. On referral to the Ophthalmology Branch of the National Institute of Neurological Diseases and Blindness, the conjunctivitis was found to be acute and nonpurulent, with lymph follicle hyperplasia, which was most marked on the lower palpebral conjunctiva. Congestion of the conjunctiva was moderately severe over the palpebral area, but minimal over the bulbar conjunctiva, and faded out toward the limbal region. There was definite discomfort, burning, and lacrimation, but without severe photophobia or pain. The palpebral fissure was narrowed moderately in the affected eye, showing blepharospasm to be present. Vision was not significantly impaired. No preauricular lymphadenopathy was noted. The eye showed no other significant abnormality except for refractive error. No involvement of the cornea could be determined.

Smears and cultures from the eyes were negative for bacteria but positive for Type 3 APC virus from the affected eye. A few mononuclear cells were present in the conjunctival smears and scrapings. No inclusion bodies were found in the scrapings. Throat swabs on the first day showed positive cultures for Type 3 APC virus and for Neisseria, nonhemolytic Streptococcus, alpha-Streptococcus, and hemolytic Hemophilus. Similar swabs three days later grew occasional Neisseria and alpha-Streptococcus colonies. The patient had been medicated only with chlortetracycline ophthalmic drops in both eyes six times daily.

No evident response to the chlortetracycline ophthalmic drops was noted, but the conjunctivitis cleared in about one week with no residual except the increased lymph follicles of the conjunctiva. No corneal involvement was noted in this case, which was the first of a series from which Type 3 APC virus has been recovered.

About two weeks after the isolation of Type 3 APC virus from the affected conjunctiva of the technician, a pediatrician was examined in our eye clinics for uniocular conjunctivitis.[8] He gave a history of onset six days after a 2-year-old girl with acute febrile nasopharyngitis and mild conjunctivitis had coughed in his face during an examination. Despite his having washed his face immediately, the infection was still suspected of association with the cough exposure. He also had rhinitis and mild pharyngitis with cervical lymphadenopathy but no preauricular adenopathy or fever.

The pediatrician's conjunctival involvement was severer than the technician's but resembled it otherwise. No corneal changes were noted, and the inflammation cleared after a week, with no noticeable response to chlortetracycline drops. As in the technician, the second eye did not give evidence of infection. It is not known whether this course was influenced by hygienic measures or the use of the eye drops. Type 3 APC virus was cultured from the affected eye and was not found in the other eye, while bacteriologic cultures were negative. No inclusion bodies were found.

Three children and three more adults who had contact with the previously mentioned child had illnesses identifiable with hers during a two-week period after her admission.[1]

To summarize the findings in these eight cases, fever for five to six days was seen in six; pharyngitis occurred in seven; rhinitis was present in seven, while in one findings were suggestive of a "common cold." Conjunctivitis was present in four cases, while five had cervical lymphadenopathy. None had preauricular lymphadenopathy. All cases gave cultures of Type 3 APC virus and/or showed a rise in neutralizing antibody titer to it. Conjunctivitis in the four cases was similar to that in the previously described cases.

Laboratory findings in the eight cases showed mild leucocytosis early in the illness with a tendency to neutrophilia. Later, differential counts became normal, with mild leucopenia developing. This series of cases occurring in a two-week period after admission of the first case failed to show any significant response to treatment with sulfonamides or antibiotics.

Fig. 1.—Nonpurulent follicular conjunctivitis in APC virus infection (mild case).

Fig. 2.—Eye in moderately severe case of pharyngoconjunctival fever.

Fig. 3.—Throat in pharyngoconjunctival fever, showing marked lymphoid hyperplasia.

Fig. 4.—Severe congestion of pharynx and throat in APC virus infection.

OBSERVATIONS ON EPIDEMICS

During the summer of 1954 outbreaks of acute catarrhal (nonpurulent) conjunctivitis with nasopharyngitis, fever, and malaise occurred in northern Virginia and the Washington metropolitan area. Some 300 cases were studied by the National Microbiological Institute and the National Institute of Neurological Diseases and Blindness.† Type 3 APC virus was recovered from some 80 of these patients, and type-specific neutralizing antibody response was found in nearly all the patients whose blood was examined.

One of the outbreaks occurred about a summer day camp near Alexandria, Va. One hundred eighty-one children 4 to 12 years of age visited this camp daily and swam or waded in its swimming pool in groups of 20 to 40 twice a day. Two other area residential communities with swimming pools also had outbreaks; one followed closely the opening of a new pool. The water in all these pools was chlorinated.

Study of home contacts of the day-camp children showed numerous cases of the disease. Adults were found less commonly affected than children. Among adults, the mothers were the ones most frequently infected. In addition to home contacts, many sporadic cases were observed, a large percentage giving a history of recent use of swimming pools.

Clinical manifestations of pharyngoconjunctival fever noted among these cases varied from one patient to another, with first one manifestation and then another predominating. An individual case might have only one or might have all known manifestations in evidence. The accompanying tabulation shows the incidence of the principal manifestations among the 80 virus-positive cases.

	%
Fever	90
Conjunctivitis	66
Sore throat	70
Headache	68
Lassitude or malaise	72

† References 3 and 9.

SUMMARY OF OBSERVED CLINICAL AND LABORATORY MANIFESTATIONS OF TYPE 3 APC VIRUS DISEASE (PHARYNGOCONJUNCTIVAL FEVER)

1. The disease occurred after an incubation period of 5 to 10 days, but averaging 1 week.

2. Spread appeared to be by many types of contact, but epidemics were associated with swimming pools even when the water was chlorinated.

3. The disease was commonest in children but often affected adults.

4. Conjunctivitis was usually associated with other manifestations, such as (*a*) nasopharyngitis, which was usually mild, but might range from slight injection of the mucosa to moderate congestion; (*b*) fever, with a temperature which might reach 104 F and last three days to two weeks; (*c*) lymphadenopathy, chiefly cervical or submaxillary, but occasionally preauricular, adjacent to the affected eye; (*d*) headaches, especially referable to the paranasal sinuses; (*e*) malaise; (*f*) sometimes gastrointestinal disturbances, and (*g*) mild leucocytosis with neutrophilia, followed by mild leucopenia.

5. Pharyngoconjunctival fever commonly had a duration of one to two weeks, but it occasionally seemed to persist longer or to recur.

6. Conjunctival symptoms most commonly ranged from itching and burning to moderately severe irritation and foreign body sensation. Photophobia might be present but was seldom severe. The ocular adnexa occasionally felt painful and were very tender. Complaints of visual blurring were rare and appeared to associate with lacrimation. Pain might occur in the ear region, with preauricular adenopathy.

7. Conjunctivitis was either uniocular or binocular, one eye often being affected some days before the other.

8. The conjunctivitis was acute and catarrhal, or nonpurulent.

9. Congestion usually affected the lower palpebral conjunctiva most, but might affect the upper palpebral and the bulbar to any degree of severity.

10. Lacrimation was usually moderate to severe, with a tendency to be intermittent.

11. Membranes or pseudomembranes were not observed.

12. Lymph follicle hyperplasia was usually present and was commonly most marked in the lower palpebral conjunctiva.

13. The cornea was not observed to be significantly affected.

14. Inclusion bodies were not observed.

15. Specific APC virus could be cultured from the affected conjunctival surfaces during active inflammation.

16. Bacterial organisms might be present in the conjunctival sac, probably as saprophytes or secondary invaders.

17. The lids might show blepharitis and/or blepharospasm.

18. The conjunctivitis was not observed to impair vision permanently.

19. The hyperplasia of lymph nodes and conjunctival lymph follicles persisted in some cases for several weeks after clearing of other signs and symptoms of the disease.

RESPONSE OF PHARYNGOCONJUNCTIVAL FEVER TO THERAPEUTIC AGENTS

No response has been noted clinically or in tissue culture to known antibiotics or sulfonamides. This observation is in keeping with properties of other known viruses of small-particle size.

Treatment of the conjunctivitis with topical cortisone or hydrocortisone, combined with antibiotic substances or sulfonamides, has been tried on a number of patients, with rapid abatement of symptoms and signs in most of them. In a small number of patients so treated, symptoms persisted to a minor degree for as long as two weeks, but with clearing of visible evidences of disease except lymph follicle hyperplasia. No cases of our study had a known exacerbation of the disease with corticosteroid treatment.

It should be remembered that evidence suggests that herpes simplex keratitis may be exacerbated by use of topical cortisone. Care must be exercised that cases of this disease be differentiated from the conjunctivitis of pharyngoconjunctival fever. Use of the biomicroscope and corneal staining with fluorescein should satisfy this need.

ISOLATION OF THE APC VIRUSES

Type 3 of the APC group of viruses, now implicated as the causative agent in pharyngoconjunctival fever, was isolated by the Virus Section of the National Microbiological Institute during its studies of causative agents of undifferentiated respiratory diseases. During the last two years some 171 strains of such viruses have been isolated,[2] at first largely by "unmasking" from adenoid and tonsillar tissue removed at surgery.[6] Later, identical or similar agents were obtained from nasopharyngeal and conjunctival secretions of persons with respiratory illnesses. Type 3 virus has been obtained only from the latter sources.

LABORATORY CHARACTERISTICS OF THE APC VIRUSES

The many strains of viruses, on inoculations of volunteers or rabbits, were found to produce group-specific complement-fixing antibodies. In addition, type-specific neutralizing antibody responses are produced. Presently, known viruses fall into eight, or possibly nine, immunologic types. It is possible that more exist.

All the types of APC viruses were found to be of small size, passing through bacteria-tight Mandler sintered glass filters with no apparent loss. They are resistant to ether, sulfonamides, and known antibiotics, greatly facilitating the clearing of contaminants from cultures by these agents. They are not heat-resistant, however, being destroyed by a temperature of 56 C for 30 minutes.

When these viruses are introduced into small laboratory animals, no clear-cut evidence of illness has been observed, though antibody response may be demonstrable in certain animals. Early inoculation of volunteers did not give significant evidence of illness. However, studies on volunteers later gave successful inoculations.

All the known types were found to be epitheliotropic, growing readily in human epithelial cells and in commercially available HeLa cells. Other tissues were found less suitable for rapid growth. In tissue culture containing both epithelial cells and fibroblasts, the viruses affect the epithelial cells first. The nuclei become indistinguishable in the large granular central portion of the cells. The cells finally become pyknotic and fall from the wall of the tube. One or two weeks is required for complete change of a sheet of epithelial cells, after which fibroblasts present are attacked, the process proceeding more slowly.

In HeLa cell cultures, densely granular rounded cells, tightly clumped or fused together, may be seen in one to three days after virus inoculation. The culture fluid tends to become more acid, causing yellowing of the phenosulfonphthalein indicator present.

SEROLOGIC SURVEYS

Early serologic surveys[2] suggested that some 50% of infants from 6 months to 1 year of age have been infected by at least one of this group of viruses. During childhood most persons appear to develop neutralizing antibodies to more than one of the known types, and by the age of 34, to at least four types. Some persons have apparently been infected by all known types.

OTHER APC VIRUSES AS A CAUSE OF CONJUNCTIVITIS

During the winter of 1954-1955 a case of bilateral conjunctivitis from which Type 4 APC virus was isolated was followed in our clinics. This occurred in a person working with Type 4 virus and is assumed to have been a laboratory infection. Nasopharyngitis was minimal, but the clinical picture was similar to the pharyngoconjunctival fever which the patient had apparently had previously. As in the Type 3 disease, the patient reported relief from conjunctival discomfort by use of a cortisone preparation.

Studies on volunteers have shown that conjunctivitis can be caused by inoculation with other types of APC viruses. Such studies are continuing on many clinical and immunologic aspects of these viruses.

SUMMARY

Collaborative work of the National Microbiological Institute, the Ophthalmology Branch of the National Institute of Neurological Diseases and Blindness, and other research agencies and individuals has brought about isolation of eight or more types of adenoidal-pharyngeal-conjunctival (APC) viruses and description of a disease entity, pharyngoconjunctival fever, associated with them.

The viruses are of small-particle size, pathogenic, and epitheliotropic, and produce specific immunologic responses. In humans the viruses can produce conjunctivitis, nasopharyngitis, fever, malaise, and lymphadenopathy.

Descriptions of ocular findings from sporadic cases and epidemics of pharyngoconjunctival fever in the metropolitan Washington area are given.

REFERENCES

1. Parrott, R. H.; Rowe, W. P.; Huebner, R. J.; Bernton, H. W., and McCullough, N. M.: Outbreak of Febrile Pharyngitis and Conjunctivitis Associated with Type 3 Adenoidal-Pharyngeal-Conjunctival Virus Infection, New England J. Med. **251**:1087-1090 (Dec. 30) 1954.

2. Huebner, R. J.; Rowe, W. P.; Ward, T. G.; Parrott, R. H., and Bell, J. A.: Adenoidal-Pharyngeal-Conjunctival Agents: Newly Recognized Group of Common Viruses of the Respiratory System, New England J. Med. **251**:1077-1086 (Dec. 30) 1954.

3. Bell, J. A.; Rowe, W. P.; Engler, J. I.; Parrott, R. H., and Huebner, R. J.: Pharyngoconjunctival Fever: Epidemiological Studies of a Recently Recognized Disease Entity, J. A. M. A. **157**:1083-1092 (March 26) 1955.

4. Cockburn, T. A.; Nitowsky, H.; Robison, T., and Cheever, F. S.: Epidemic Keratoconjunctivitis: A Study of a Small Epidemic, Am. J. Ophth. **36**:1367-1372 (Oct.) 1953.

5. Cockburn, T. A.: An Epidemic of Conjunctivitis in Colorado, Associated with Pharyngitis, Muscle Pain and Pyrexia, Am. J. Ophth. **36**:1534-1539 (Nov.) 1953.

6. Rowe, W. P., and others: Isolation of Cytopathogenic Agent from Human Adenoids Undergoing Spontaneous Degeneration in Tissue Culture, Proc. Soc. Exper. Biol. & Med. **84**:570-573 (Dec.) 1953.

7. Hilleman, M. R., and Werner, J. H.: Recovery of New Agent from Patients with Acute Respiratory Illness, Proc. Soc. Exper. Biol. & Med. **85**:183-188 (Jan.) 1954.

8. Rowe, W. P.; Huebner, R. J.; Hartley, J. W.; Ward, T. G., and Parrott, R. H.: Studies of Adenoidal - Pharyngeal - Conjunctival (ABC) Group of Viruses, Am. J. Hyg. **61**:197-218 (March) 1955.

9. New Type of Virus Conjunctivitis Described, Sight-Saving Rev. **24**:216, Winter, 1954.

10. Derrick, E. H.: Swimming-Bath Conjunctivitis, with Report of 3 Probable Cases and Note on Its Epidemiology, M. J. Australia **2**:334-336 (Oct. 23) 1943.

11. Neva, F. A., and Enders, J. F.: Isolation of a Cytopathogenic Agent from an Infant with a Disease Resembling Roseola Infantum, J. Immunol. **72**:315-321 (April) 1954.

Cataract Surgery in Megalocornea

Report of Case of Two Extractions and Review of Cases Since 1931

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Megalocornea, or anterior megalophthalmus, is a bilateral inherited developmental anomaly found almost entirely in males, in which the intraocular tension is not above normal, the corrected visual acuity is normal, and the anterior segment of the eye is larger than normal.* It is usually inherited as a sex-linked recessive trait, but may occasionally be due to an incompletely dominant gene.[4]

The differentiation of megalocornea and buphthalmos or hydrophthalmos is not difficult if one is aware of this rare condition. In megalocornea both corneas are enlarged, with horizontal diameters of from 13 to 18 mm., and the intraocular tension and corrected visual acuity are normal. In buphthalmos and hydrophthalmos the corneas are also enlarged (35% unilaterally), the intraocular tension is above normal until treated, and the corrected visual acuity is often not normal.

Kestenbaum's[5] table differentiating megalocornea and buphthalmos is translated in Duke-Elder's "Text-Book"[2] and in Vail's widely quoted article on megalocornea.[1]

The four major signs of megalocornea are (*a*) enlarged transparent corneas (with vision correctible to normal); (*b*) hereditary or familial incidence; (*c*) occurrence always bilateral and almost exclusively in males, and (*d*) absence of all evidence of glaucoma.[1] Our case fulfilled these four major criteria and had five of the several minor characteristics of megalocornea: (*a*) deep anterior chambers; (*b*) poor dilatation of the pupils; (*c*) embryotoxon; (*d*) cataracts, and (*e*) sharply defined corneoscleral margins.

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* References 1 and 2.

REPORT OF CASE

C. S., a 50-year-old white farmer, was first seen at the University of Minnesota Hospitals (#854,987) in September, 1952.

Chief Complaint.—"I have a cataract in my left eye, and my right eye is crossed."

Present Illness.—Both eyes always were "too big." Neither eye had been inflamed or painful except after an injury to the right eye with a stick (contusion ?) at the age of 15. Vision up to this time was believed to be normal in each eye. The right eye recovered quickly after the injury, but about a year later the right eye "turned in." The right eye had not been used since the age of 16, and vision in the left eye had gradually failed in the last two years.

Family History.—Five sisters, all with normal eyes. One brother, with good corrected vision, had large eyes like the patient's and died of tuberculosis, aged 38. The father was said to have large eyes but did not wear glasses.

System Review.—Moderately decreased hearing since birth. Remaining 18 teeth were bad (and were removed prior to surgery).

Physical Examination.—Vision: O. D.: Good light projection and two-point light discrimination; O. S.: 20/300, improved to 20/200 with +1.25 D. sph. Both eyes appeared large. The horizontal diameter of the right cornea was 17 mm. and that of the left 15 mm. There was 45△ of right concomitant strabismus. Embryotoxon was seen at each limbus from 5 to 7 o'clock. I. O. T. 16 mm. Hg (Schiøtz) O. U. The anterior chambers appeared abnormally deep, and the pupils dilated poorly with 2% homatropine. Corneoscleral margins were sharply defined. The corneas were thinner than normal. Senile immature cataracts O. U., the right more advanced

than the left. Opacities cuneiform in type and cortical in location. Poor red reflex O. D.; good red reflex O. S.; no fundus detail seen.

Hospital Course.—On Oct. 2, 1953, I performed a complete iridectomy and intracapsular cataract extraction on the right eye, without loss of vitreous or other complication. A sliding fornix-base conjunctival flap was made above. A preplaced corneoscleral mattress suture at 12 o'clock was of 6-0 double-armed silk. After the horizontal bite at 12 o'clock, one-half of the thickness of the cornea, nearly horizontal episcleral bites were taken with the two free arms just across the limbus from the exits of the silk from the cornea. The two free arms were then passed up through the conjunctival flap at 12 o'clock, so that, when tied later, the corneoscleral suture aided in holding the flap over the section. This preplaced suture, as well as over-all strategy, was suggested by Dr. Erling W. Hansen, Director of the Division of Ophthalmology, University of Minnesota, and is a modification of the Stallard suture.[6] The latter, in turn, is a modification of the first corneoscleral preplaced suture devised by Kalt in 1894.[7] The section was made with a keratome and completed to 3 and 9 o'clock with McGuire scissors. The cornea was noted to be considerably thinner than normal. Complete iridectomy was done. The lens was easily delivered with Castroviejo capsule forceps and Smith expressor hook. The iris pillars were reposited with an iris spatula, and the 12-o'clock preplaced suture, which had been pulled up after cataract extraction, finally tied. Two preplaced limbal sutures at 3 and 9 o'clock were then used to pull the sliding fornix-base conjunctival flap down over the section. The two limbal sutures at 9 and 3 o'clock were removed in 14 days, but the corneoscleral 12-o'clock suture was not removed until the 22d day, because of the abnormally thin cornea noted at surgery. Two months after surgery the vision in the right eye was 20/30 with a + 9.00 sph. ⊖ + 1.75 cyl, axis 180.

On Nov. 13, 1953, Dr. E. S. Palmerton removed the cataract in the left eye, using the same technique. The extraction was an attempted intracapsular one, but the capsule ruptured and the surgeon felt this was probably due to the tip of his keratome touching the anterior capsule. Almost all the lens remnants were irrigated out. The left eye healed without event until the 11th postoperative day, when the three sutures were removed. A partial hyphema appeared immediately but cleared spontaneously in a week. Atropine was instilled at the time of surgery and instillations continued daily. The treatment of hyphema is still a controversial problem.[8] Within a week after the sutures had been removed a cleft appeared at the limbus from 10:30 to 1 o'clock. This area never stained with fluorescein; the chamber remained deep, and this healing defect remained covered with conjunctiva and disappeared in two months. At the periphery the right pillar of the iris became attached to the posterior surface of the incision at 11 o'clock and the pupil over a year's time became displaced upward 2 mm. Two months after surgery corrected vision O. S. was 20/25. Eight months later vision O. S. was 20/20 with +9.50 sph. ⊖ + 1.00 cyl, axis 170. Both fundi after surgery appeared normal.

Although the right eye had been esotropic for 24 years, corrected vision O. D. two months after surgery was 20/30. Vision in this eye remained good postoperatively (one year certain), but the right eye returned to its esotropic position after the successful cataract surgery on the left eye. The minor complication of partial corneoscleral separation from 10:30 to 1 o'clock in the left eye may have been due to the removal of the corneoscleral suture on the 11th postoperative day, as against the 22d day in the right eye.

The modified Kalt-Stallard corneoscleral sutures used in these two extractions produced very satisfactory results, although I presently prefer McLean type sutures [7] which are being employed alternately with 6-0 mild chromic gut † and 6-0 silk.

COMMENT AND REVIEW OF LITERATURE

Vail [1] in 1931 completely reviewed the literature on megalocornea. He reported 69 carefully studied cases. Of these 69 cases, 27, or 39%, had lens opacities. There had been 18 cataract extractions reported by eight men up to 1931. Twelve of these 18 operations resulted in "useful vision." In 15 of the 18 extractions the surgeon mentioned whether or not he had lost vitreous. In 7 of these 15 cases vitreous was lost and may well have been lost in 3 others, and thus one-half to two-thirds of these cases lost vitreous.

Since 1931 eight cataract extractions in six cases of megalocornea have been reported ‡ (Table).

Each report concerned one extraction, except for the case of Savin [3] and that of Vos,[14] in which both cataracts were removed. The extractions in our cases bring to 10 the number of cataract extractions performed in seven cases of megalocornea, and reported

† References 9 and 10.

‡ References 3 and 11 through 15.

Summary of Cataract Extractions Since 1931 in Patients with Megalocornea

Extraction No.	Surgeon	Age	Sex	Type of Delivery	Vitreous Loss	Preoperative Vision	Postoperative Vision	Comment
1	Vell and Sarrazin [11]	51	M	Intracapsular	None	L. P.	8/10	.....
2	Posthumus [12]	39	M	Extracapsular	Yes	L. P.	8/10	Long postoperative inflammation; needling required
3	Klar [13]	43	M	Intracapsular	None	L. P.	5/7	Iris prolapse 10 days postoperative
4	Savin [3]	58	M	Intracapsular	None	Light and motion	Good light projection	Old macular lesion found postoperative
5	.....	..	..	Intracapsular	None	L. P.	8/9	Complete iridectomy (same patient as in no. 4)
6	Vos [14]	51	M	Extracapsular	?	L. P.	5/5	No. 6 and no. 7 on same patient; vision known by surgeon to be normal in both eyes 11 yr. preoperatively
7	.....	..	..	Extracapsular	Yes	L. P.	5/6	
8	Hamilton [15]	?	M	?	?	?	?	Eye lost soon postoperatively
9	Smillie	50	M	Intracapsular	None	Light projection	20/30	Right esotropia 24 yr. preoperative; no. 9 and no. 10 on same patient
10	Palmerton	50	M	Extracapsular	None	20/200	20/20	.....

since 1931. Nine of these 10 cataract extractions since 1931 resulted in useful vision (Table). One eye was lost from spontaneous retinal detachment on the 10th postoperative day.[15] Vitreous was lost in two of the eight cases since 1931, in which this fact was reported.

Though these two series are too small for statistically significant comparison, there seems to have been a definite improvement since 1931 in the results of cataract surgery in megalocornea. Useful vision resulted in 66% of the extractions before 1931 and in 99% of the extractions after 1931. Vitreous loss occurred in one-half of the extractions before 1931 and in but one-quarter of them since.

Davies [16] has reported an interesting case of megalocornea with cataracts in which, in one eye, the lens was subluxated to such an extent that it tipped over completely backward and was suspended by the zonule at 6 o'clock. In his case operation was not necessary, as a aphakic correction gave good vision in this eye.

Savin [3] gave as his reasons for attempting intracapsular extractions the fact that tremulous lenses, as well as iridodenesis, are frequently seen in megalocornea. He successfully performed intracapsular extraction without vitreous loss in either eye. The two instances in which vitreous was lost after 1931 § were cases in which intentional extracapsular extractions were done.

SUMMARY

A case of megalocornea complicated by cataracts is reported. The cataracts were successfully removed without loss of vitreous, and good vision resulted in each eye. Cases of megalocornea with cataract surgery recorded up to 1931 are reviewed.[1] The literature on megalocornea since 1931 has been reviewed to find and discuss those cases in which cataract surgery has been done since then.

Useful vision resulted in 66% of the 18 cataract extractions performed before 1931 in patients with megalocornea, and in 90% of the 10 extractions in cases of megalocornea reported since then.

Vitreous loss occurred in one-half the cataract extractions in megalocornea before 1931 and in one-fourth of the extractions reported since then.

Cataract extractions in megalocornea have often been complicated by vitreous loss and poor results,‖ but cases should be reported in any event.[3]

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§ References 12 and 14.

‖ References 1 and 2.

REFERENCES

1. Vail, D. T., Jr.: Adult Hereditary Anterior Megalophthalmus sine Glaucoma: A Definite Disease Entity; with Special Reference to the Extraction of Cataract, Arch. Ophth. **63**:39-62, 1931.

2. Duke-Elder, W. S.: Megalocornea, in Text-Book of Ophthalmology, Vol. II, St. Louis, C. V. Mosby Company, 1938, p. 1277.

3. Savin, L. H.: A Note on 2 Cases of Megalocornea, Brit. J. Ophth. **26**:263-271, 1942.

4. Falls, H. F.: Clinical Detection of the Genetic Carrier State in Ophthalmic Pathology, Am. J. Ophth. **37**:841-854, 1954.

5. Kestenbaum, A.: Megalocornea, Klin. Monatsbl. Augenh. **62**:734-752, 1919.

6. Stallard, H. B.: A Corneo-Scleral Suture in Cataract Extraction: Its Techniques and Advantages, Brit. J. Ophth. **22**:269-273, 1938.

7. McLean, J. M.: A New Corneoscleral Suture, Arch. Ophth. **23**:554-559, 1940.

8. Smillie, J. W.: Effect of Streptokinase on Simulated Hyphema, with a Study of Its Toxicity to Anterior Chambers of Rabbits, Am. J. Ophth. **37**:911-917, 1954.

9. Fralick, F. B.: 6-0 Chromatized Gut in Wound Closures After Cataract Extraction, West Virginia M. J. **46**:251-255, 1950.

10. Dunnington, J. H., and Regan, E. F.: Absorbable Sutures in Cataract Surgery, A. M. A. Arch. Ophth. **50**:545-556, 1953.

11. Veil, P., and Sarrazin, L.: Hereditary and Familial Megalocornea, Ann. ocul. **176**:241-252, 1939.

12. Posthumus, R. G.: Megalocornea in Its Relationship to Other Deviations in Members of the Same Family, Klin. Monatsbl. Augenh. **102**:1-14, 1939.

13. Klar, R.: Contribution to the Question of Megalocornea in Relation to Patients Operated on for Cataract and Their Families, Klin. Monatsbl. Augenh. **104**:286-299, 1940.

14. Vos, T. A.: Megalocornea Cataract, Ophthalmologica **120**:248-250, 1950.

15. Hamilton, J. B.: Megalocornea and Its Surgical Complications, Australian & New Zealand J. Surg. **20**:184-187, 1951.

16. Davies, W. S.: Megalophthalmus: Report of a Case, Am. J. Ophth. **18**:542-544, 1935.

Acetazoleamide (Diamox) in Glaucoma Surgery

Acetazoleamide in the Treatment of Flat Postoperative Anterior Chamber Following Glaucoma Surgery

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This report deals with five patients in whom nine eyes had surgery performed for control of primary elevated intraocular pressure. Filtering operations are most frequently employed for this purpose.

Delayed restoration or flatness of the anterior chamber which develops after filtering and other antiglaucoma operations is sometimes followed by a serious postoperative complication. The usual result is formation of goniosynechiae and block of the trabecular drainage area. The incidence of delayed chamber restoration or of flat anterior chamber developing several days after cataract surgery is relatively infrequent, varying from 4% to 10%. Delayed chamber restoration after filtering glaucoma operations, unfortunately, occurs rather often (30% to 50% of cases).

A peripheral iridectomy performed in prodromal narrow-angle glaucoma (as a prophylactic measure) with controlled tension may at times be followed by the presence of a flat postoperative anterior chamber for several days. The patient may develop circumferential goniosynechiae, which may not have existed before surgical intervention. To avoid this complication, the surgeon frequently closes the limbal or scleral incision by means of an interrupted suture. Such closure usually prevents the delayed restoration of the chamber, but it does not routinely result in its prompt reestablishment.

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Becker * explained the hypotensive action of acetazoleamide (Diamox) by the inhibition of aqueous humor secretion. This concept has been seconded by Grant and Trotter [3] clinically and confirmed by Green, Capper, Bocher, and Leopold [4] experimentally.

I † have previously reported on the therapeutic use of acetazoleamide for glaucoma and also for the restoration of nonleaking flat and shallow anterior chamber associated with early choroidal detachment following cataract extraction. The administration of this drug in large doses resulted in early restoration of the chamber in the large majority of such instances in the group operated on for cataract.

On the basis of this experience, it was decided to try acetazoleamide in cases of glaucoma surgery with the purpose of observing its effect on restoration of postoperative flat anterior chamber and on the healing of the incisional filtration area. Observations were made on nine eyes operated on in five glaucomatous patients.

These cases fall into two groups:

1. In three patients (four eyes operated on) the drug was used with therapeutic

* References 1 and 2.

† Thorpe, H. E.: Diamox in Primary and Secondary Glaucoma, read at a meeting of Cincinnati Ophthalmological Society, Feb. 10, 1954; Carbonic Anhydrase Inhibitor as a Therapeutic Agent in Ophthalmology, read at a meeting of the Association for Research in Ophthalmology, Eastern Section, Philadelphia, Feb. 18, 1954; Diamox in the Treatment of Nonleaking Flat Anterior Chamber Occurring After Cataract Extraction, read at the 17th International Congress of Ophthalmology, New York, Sept. 17, 1954.

intent after the anterior chamber had been observed to be flat for two or more days.

2. In five other eyes operated on the drug was used as a prophylactic measure (this included the fellow eye of one of the patients in the first group). This small series includes the eyes of four patients on which I operated and of one patient who was under the care of Dr. A. Krieger.

Iridencleisis was performed on six eyes afflicted with narrow-angle glaucoma (this operation is frequently attended by delayed chamber restoration). Cyclodialysis was performed on one aphakic eye. Cataract extraction was performed in both eyes of a patient with capsular exfoliation and open-angle glaucoma.

METHOD OF ADMINISTRATION

When used with therapeutic intent, acetazoleamide was administered in cases of flat chamber two to four days after surgery. It was administered orally with a first dose of 250 to 1000 mg., followed by 250 mg. of the drug every six hours for three to seven days.

When used with prophylactic intent, administration of the drug was commenced within four to six hours after surgery and continued for several days. The dosage was similar to that indicated above.

REPORT OF CASES

Case 1.—J. A., man, age 73; "open-angle glaucoma"; capsular exfoliation of both crystalline lenses; immature senile cataracts. Intraocular pressure was originally controlled by miotics, later aided by acetazoleamide administration; finally it failed to be controlled by combined use of miotics and acetazoleamide. Preoperative intraocular pressure varied: O. D., 37 to 43 mm. Hg; O. S., 25 to 30 mm. Hg. Visual acuity: O. D., 20/200; O. S., 20/200+. Bilateral glaucomatous cupping of optic disc. Marked concentric contraction of visual fields. Trabeculum visible and covered in lower portion by dandruff-like debris. On April 13, 1954, the right eye was operated on—intracapsular cataract extraction combined with basal iridectomy (sector of iris sphincter excised to root). On May 6, a combined intracapsular extraction was performed on the left eye. The patient was maintained on acetazoleamide administration throughout his preoperative and postoperative period. Five scleral sutures were used in each eye (scleral incision and limbus-based conjunctival flap). The incisions healed uneventfully. The anterior chambers were found restored at the first and at subsequent dressings. Since surgery the intraocular pressure has varied between 12 and 20 mm. Hg in the right eye and between 12 and 23 mm. Hg in the left eye. Visual acuity is 20/20, O. D., and 20/30, O. S. The trabeculum could be readily seen with the gonioscope in each eye after surgery.

Case 2 (Dr. Krieger's patient).—N. C., man, age 39; narrow-angle glaucoma, noncongestive state. Preoperative intraocular pressure: O. D., 40 mm. Hg; O. S., 40 mm. Hg. Visual acuity: O. D., light perception; O. S., 20/40. The left visual field showed concentric contraction. The fundi revealed bilateral glaucomatous cupping of the optic disc. Gonioscopy revealed that the trabeculum was obscured by iris rolls. Iridencleisis was performed on the right eye by Dr. Krieger on June 10, 1954. The anterior chamber remained flat for four days. On my advice, 750 mg. of acetazoleamide was administered and its use continued in routine dosage of 250 mg. The right anterior chamber was found restored the day after acetazoleamide administration was begun. Iridencleisis was performed on the left eye on June 16, 1954, while the patient was under acetazoleamide treatment. When the eye was dressed on June 17, the chamber was found restored. Both anterior chambers have maintained their depth. Postoperative intraocular pressure has remained at 17 mm. Hg. A rather small filtration bleb is now present in each eye.

Case 3.—Mrs. J. P., age 60; bilateral endothelial dystrophy; narrow-angle glaucoma in noncongestive state. The intraocular pressure read 45 mm. Hg, O. D., and 75 mm. Hg, O. S. (while the patient was under miotic treatment). It was reduced with the aid of acetazoleamide to 18 mm. Hg, O. D., and 17 mm. Hg, O. S., but rose again to 55 and 20 mm. Hg, respectively. The corneal diameters measured 11 mm. The anterior chambers were quite shallow. The visual acuity was 20/40, O. D., and 20/30, O. S. Both blind spots were enlarged. The optic discs showed moderate central cupping. Gonioscopy showed that the trabeculum was obscured by iris rolls. The patient was continued on acetazoleamide administration, 250 mg. every six hours, before and after operation. On Oct. 14, 1954, iridencleisis was performed on the right eye, and on Oct. 19, on the left eye. The anterior chambers were found to be restored the day following surgery. They have remained established, but shallow, to the present time. The postoperative intraocular pressure has varied between 16 and 20 mm. Hg in the right eye and 13 and 14 mm. Hg in the left eye. The patient

continued to take acetazoleamide in doses of 250 mg. every six hours continuously, while living in another city. On April 19, 1955, filtration areas showed no bleb formation. Visual acuity is 20/25, O. D., and 20/50, O. S. The trabeculum could be visualized in the lower quadrant in each eye.

CASE 4.—Mrs. J. K., age 54; diagnosis: narrow-angle glaucoma, noncongestive state. The preoperative intraocular pressure was 46 mm. Hg, O. D., and 40 mm. Hg, O. S. Visual fields revealed nasal quadrant defect. Visual acuity was counting fingers at 1 ft., O. D., and 20/50—1, O. S. There was bilateral glaucomatous cupping of the optic disc. On gonioscopic examination, the trabeculum was found to be obscured by the iris periphery. Bilateral iridencleisis was performed on Oct. 16, 1954. On Oct. 17, at the first dressing, both anterior chambers were flat and remained so for two days. On Oct. 18, acetazoleamide, 1000 mg., was administered orally and continued in 250 mg. dosage every six hours for one week. On Oct. 19, the right anterior chamber was shallow and the left anterior chamber was more fully formed. On Oct. 24 both chambers were formed and have continued so. The intraocular pressure has remained below 20 mm. Hg in each eye. The filtration area shows very little bleb formation. The trabeculum could be visualized in the upper and lower quadrants.

CASE 5.—Mrs. M. M., age 52; diagnosis: former bilateral malignant glaucoma with bilateral aphakia (O. S., absolute glaucoma). Both crystalline lenses had been removed in October, 1953, after previous glaucoma surgery for bilateral malignant glaucoma. After staying under varying degrees of control with use of intensive miotic and acetazoleamide therapy, the intraocular pressure rose, reaching 51 mm. Hg, O. D., and 70 mm. Hg, O. S. Visual acuity was 20/30, O. D., and 0, O. S. The visual field test showed marked concentric contraction on the right and no field on the left. There was marked glaucomatous cupping of both optic discs. Gonioscopy revealed an obstructed chamber angle in each eye. On Feb. 1, 1955, cyclodialysis was performed on the right eye in the lower quadrant, between 4 and 8 o'clock. Cyclodiathermy by Weekers' technique was performed on the blind (left) eye. Acetazoleamide, 250 mg., was administered orally every six hours during the postoperative period. The anterior chamber in each eye remained formed throughout this period. The intraocular pressure, after three and a half months, is 10 mm. Hg, O. D., and 55 mm. Hg, O. S. Visual acuity is 20/25 in the right eye; the left eye is amaurotic. Gonioscopy reveals an open cyclodialysis cleft below in the right eye.

RESULTS AND COMMENT

The use of acetazoleamide in three cases of flat anterior chamber of several days' duration following iridencleisis resulted in restoration of the chamber in about 24 hours. This effect included the right eye in Case 2 and both eyes in Case 4. The fellow eye in Case 2 had an iridencleisis performed while under acetazoleamide therapy. It never developed a flat chamber. That this complication was avoided might be considered as a prophylactic effect of acetazoleamide against flat anterior chamber.

Case 4 had bilateral iridencleisis performed while under acetazoleamide therapy and consistently had an anterior chamber during the convalescent period. This case, too, might be considered as having avoided a flat chamber because of acetazoleamide use. However, spontaneous regeneration of the chamber is entirely possible.

Case 1 had a bilateral combined intracapsular cataract extraction for glaucoma associated with capsular exfoliation while under acetazoleamide administration. The anterior chambers remained formed throughout the postoperative period.

Case 5, in which a cyclodialysis was performed on the right eye in aphakic glaucoma, retained a formed anterior chamber while under acetazoleamide therapy.

Cases 1 and 4 are still on minimal acetazoleamide therapy.

Cases 2, 3, and 4, with iridencleisis performed in each eye, showed minimal filtration bleb formation at the site of surgery.

The restoration of the flat postsurgical chamber may be due to the abstraction of fluid from the subchoroidal spaces because of diuresis, or it may be brought about by reduced aqueous humor secretion into the subchoroidal spaces or by the facilitated earlier closure of a leaking filtration wound.

CONCLUSION

It appears from this rather small series of cases of glaucoma surgery that acetazoleamide (Diamox) administration during the postoperative period is conducive to early restoration of the anterior chamber and to

maintenance of a formed chamber. The series is too small to rule out coincidental spontaneous chamber restoration.

It also appears that the lowered intraocular pressure incident to inhibition of aqueous humor secretion by acetazoleamide may lead to minimal cystic filtration bleb formation in the surgical drainage area. Its use may therefore be inadvisable in these cases.

There is as yet no definite proved physiological explanation for the action of acetazoleamide in restoration of the anterior chamber after intraocular surgery.

Jenkins Bldg. (22).

REFERENCES

1. Becker, B.: Decrease in Intraocular Pressure in Man by Diamox, Am. J. Ophth. **37**:13-15 (Jan.) 1954.

2. Breinin, G. M., and Gortz, H.: Carbonic Anhydrase Inhibitor Acetazoleamide, A. M. A. Arch. Ophth. **52**:333-346 (Sept.) 1954.

3. Grant, W. M., and Trotter, R. R.: Diamox in Treatment of Glaucoma, A. M. A. Arch. Ophth. **51**:735-739 (June) 1954.

4. Green, H.; Capper, S.; Bocher, C., and Leopold, I. H.: Effect of Acetazoleamide (Diamox) on Carbonic Anhydrase Activity of Anterior Uvea of the Rabbit Eye, A. M. A. Arch. Ophth. **52**: 758-761 (Nov.) 1954.

The Fundus Oculi in Monozygotic Twins

Report of Six Pairs of Identical Twins

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Twins have aroused the curiosity of man throughout history. In modern times twin research has become a special branch of human genetics and has greatly contributed to our knowledge of the earliest stage of prenatal development. Another aspect of twin research is the distinction between inherited and acquired traits. Of particular value are observations in monozygotic (true, single-egg) twins, who originate from one chorion and a single placenta. They are always of the same sex and belong to the same blood group; their over-all resemblance is very close, and popularly they are known as identical twins.

Twin research in ophthalmology has assumed considerable proportions. Every normal and abnormal eye trait in identical twins has been extensively investigated, and a number of studies are especially devoted to findings in the fundus oculi. Yet there still is very little agreement among the most competent observers, some claiming complete identity of all characteristic features,[14] others excluding the fundus of the eye from the scope of twin research.[40] Considering this state of affairs, it may be permissible to review the question of the eyeground in identical twins and to present ophthalmoscopic observations in six pairs.

A brief glance at recent contributions dealing with other ocular traits in monozygotic twins will make it plain that lack of agreement is not limited to the eyeground. Hofstetter and Rife[18] arrived at the conclusion that the type of twinship cannot be identified on the basis of optometric examination. Occasionally an extreme discrepancy in refraction of identical twins has been observed, as, for instance, by Orth,[26] who found one of two brothers emmetropic, while the other had myopia of 25 D. Marked differences in refraction occur even in the presence of essentially similar squint; a case of this type has been reported by Masters:[20] In a pair of full-term monozygotic twins, with a single placenta, the right eye of one twin presented a definitely pathologic error, while in the other twin there was only a slight departure from normal. Such findings disagree with the statement of Gates[9] that in identical twins the range of variations in refraction is narrow, nor are they in accord with Waardenburg,[40] who maintains that evidence points to a hereditary basis of refraction and errors of refraction.

Within the framework of the present investigation, findings concerning myopia in identical twins are of particular interest, due to the associated fundus changes. In a pair of identical male twins, seen by Meyer-Schwickerath,[22] the degree of myopia was less in one eye than in the three others; accordingly, the diameter of the circumpapillary conus was smaller in that eye, and choroidal atrophy not so pronounced. The hereditary character of myopia becomes clearly apparent in a set of identical male twins with high compound myopic astigmatism in their right eyes and congenital complicated cataract in both left eyes; in these fundi there was pallor of the disc, but Constans[5] observed retraction of the scleral ring only in the one boy who presented other congenital defects, not encountered in his twin, particularly

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congenital cleft palate. Still more interesting is a pair of 51-year-old female monozygotic twins with high myopia, reported by Burns.[3] Refraction in the right eye showed close similarities, while there were significant differences in the left eyes. Nevertheless, in all four eyes there was high myopia, with extensive choroidal atrophy at the posterior pole. All four fundi, though not identical as to vascular pattern and features of the disc, presented very close resemblances; yet spontaneous venous pulsation was limited to both eyes of one twin. A pair of female monozygotic twins studied by Hofmann and Carey [12] showed a high degree of compound myopic astigmatism, and the similarity of ocular traits extended to the lids, the palpebral fissures, the eyebrows, and the eyelashes; the shape and size of the disc and the color of the retina corresponded closely, but the distribution of the blood vessels was markedly different: In one of the twins all principal vessels were crowded into the nasal half of the disc, without comparable findings in the other twin.

According to Waardenburg,[39] convergent strabismus in uniovular twins is mostly similar. Of particular interest is a case reported by Pillat.[27] A pair of Chinese monozygotic twins presented mirror-like symmetry, not only with regard to monocular strabismus, but also in the fundus pictures. In both twins the optic papilla of the nonsquinting eye was normal, round, and encircled by a scleral ring; the squinting eye, on the other hand, showed oblique entry of the optic nerve, with an oval papilla, and physiologic excavation projecting on the nasal side, with vessels leaving the papilla in an oblique direction; there was a crescent due to supertraction, and choroidal atrophy temporally and below.

Many case reports, primarily concerned with other ocular conditions in twins, contain interesting fundus findings. For instance, Glover [11] observed in a pair of identical twins with amblyopia that, among other common traits, all four optic discs "were oval at 90 degrees." Rychener [29] found that in all four eyes of identical twins the first branching of the vessels at the optic disc occurred at an elevated level, due to profuse colloid deposits, which covered all other landmarks of the disc and projected slightly into the retina; the finding is interpreted as a congenital anomaly without pathologic significance. Vogt [36] stressed the similarity of senile changes in the fundi of monozygotic twins, particularly the development of circumpapillary choroidal atrophy and drusen of Bruch's membrane. Oberhoff [25] observed in a pair of hyperopic twins, described as stunningly similar, a slight degree of pseudoneuritis in all four eyes. Vogelsang,[35] who reported macular coloboma in the right eyes of a pair of monozygotic twins, found no similarities in the course of the fundus vessels. Waardenburg [39] stated that with regard to the emergence of the vessels at the papilla concordance and discordance balance each other.

Gesell and Blake [10] examined the eyegrounds of identical female twins; all four were of the blond type, with the choroidal vessels plainly visible toward the periphery. Both twins presented slightly atypical colobomas of the macula, which were strikingly alike in all four eyes; but, in spite of this over-all similarity, the retinal vessels traversed the central lesion only in one of the four eyes, indicating a discordant vascular pattern. Badtke [1] detected in a pair of monozygotic twins with mirror symmetry of esophoria and hypermetropic astigmatism, that all four optic discs were round and peach-colored; a small temporal pigmentary crescent in the left eye of the one twin and in the right eye of the other also showed mirror symmetry, but there was no significant similarity in the distribution of the fundus vessels. According to Fowler,[7] the pattern of the retinal vessels was dissimilar in two pairs of identical twins; one of them exhibited a pigmentary defect alongside the disc of one eye, without comparable findings in the other eye, or in the other twin. Ida Mann examined the fundi of a pair of monozygotic twins with situs inversus of the

viscera, reported by Cockayne [6]; she found the retinal arterial patterns dissimilar in all four eyes and mentioned that no similarity of vascular arrangement should be expected in the corresponding or opposite eyes of monozygotic twins.

Apparently, the first study exclusively dedicated to an investigation of the fundus in twins is by Huber.[14] He examined 16 pairs of monozygotic and 7 pairs of fraternal twins, ranging in ages from 6 to 34 years. Huber came to the following conclusion:

> With regard to shape, color and physiologic excavation of the papilla, and furthermore, pigment and scleral crescents, color of the fundus, and peripheral and retinal vessels, the monozygotic twins are strictly identical (*stimmen haargenau überein*).

The statement that the vascular pattern in monozygotic twins shows complete identity is surprising. The photographs are too small to permit a recheck, but the accompanying legends do not bear out Huber's generalization in the summary. In some pairs course, arrangement, distribution, and number of the principle retinal vessels show no more than a fair degree of similarity; at other times the legend seems to indicate even less correspondence. It is significant, furthermore, that when Vogt and his co-workers [37] reviewed the findings of Huber, who had been working under Vogt, reference to the identity of the vascular patterns was omitted, while all other statements were endorsed, especially the marked similarities of the various features of the optic papilla.

Stern [31] carried out a detailed examination of the fundi of 12 pairs of twins. He found no corresponding traits in the retinal veins, and even the arteries were not similar to the point where divergencies could be demonstrated by placing one photograph on top of the other. Stern therefore made precise notations of each fundus, in an attempt to obtain values equivalent to anthropometric measurements. On that basis, he arrived at the conclusion that no essential concordance exists in the distribution of the fundus vessels in monozygotic twins. On the other hand, shape and size of the papilla, the color of the fundus as a whole, and the degree of physiologic excavation were found to be consistently identical in the corresponding eyes of all twins, whether monozygotic or fraternal. Concordance was also observed in such congenital abnormalities as temporal conus, scleral ring, and atypical entry of vessels. Franceschetti and Klein [8] mentioned that the fundus as a whole is very similar in uniovular twins; yet the pattern of the vessels at the papilla presents differences analogous to those of the cutaneous ridges of the finger tips, and therefore might serve for purposes of identification. Lehrfeld [17] maintained that in homologous twins the principal trunks of the retinal arteries branch bilaterally within the disc border, and that vascular branchings are altogether more numerous.

The literature, therefore, shows almost complete agreement concerning the similarity of the optic disc in monozygotic twins, while the pattern of the retinal vessels is generally regarded to be dissimilar; little attention has been given to the central area, except in the presence of definite anomalies, such as, for instance, coloboma of the macula.

MATERIAL AND METHOD

Six pairs of identical twins were studied by means of ophthalmoscopic examinations and fundus photographs (Figs 1 to 6). The youngest pair was 3½ years of age; the oldest, 82. In each age group, one pair was male, the other female. Monozygosity was assumed on the basis of sex, external similarity, and such general signs as color of iris, history, etc. In Pair 2, the pattern of the freckles was an additional indication, and both twins of Pair 3 are hemophiliacs.

It is commonly recognized that no verbal description suffices, in view of the extreme variability of fundus appearances. In order to establish a basis of comparison, however, the findings in all eyes have been classified under 11 headings and presented in the legends to the fundus photographs. The first five headings refer to the disc and its immediate environment; the following three headings, to the macular region; the next two headings are related to the general impression of the retina, while findings concerning the retinal vessels are combined under a final heading. It is fully realized that such an arrangement is arbitrary, and the same criticism applies to the estimate of degrees of similarity or

Fig. 1 (Pair 1).—Bry. T. (*A*), and Bre. T. (*B*), identical twins, 3½ years old.

1. Optic Disc: Both right eyes: slightly oval; both left eyes: almost circular.

2. Physiologic excavation: All four eyes: shallow.

3. Disc margin: Slight pigmentary crescent, temporally, in both eyes of *A*, and in right eye of *B*, absent in *B*, left.

4. Pattern of vessels emerging from disc: *A*, right, and *B*, left: separating well below surface. *A*, left: just below surface. *B*, right: just above surface of disc.

5. First branching of arteries and veins: In *A*, right, and in both eyes of *B*: within disc. In *A*, left: just beyond disc margin.

6. Macula: All four eyes: deep dark. No central reflex.

7. Perimacular area: In *A*, right, and *B*, left: wide dark zone; in *A*, left, and *B*, right: less well marked.

8. Perimacular reflex: In *A*, right, and *B*, left: round, total, pronounced; in *A*, left, and *B*, right: small, localized.

9. Fundus in general: All four eyes: light-colored fundus. Choroidal landmarks clearly indicated, as common in children.

10. Reflexes: In *A*, right, and *B*, left: pronounced, particularly in temporal half. In *A*, left: almost absent; in *B*, right: moderately marked.

11. Retinal vessels: In *A*, right, and *B*, left: similar branching of superior temporal vein, but angle more acute in *B*, left. In *A*, right, and *B*, left: slight similarity of vascular pattern; some similarity also in two right eyes, particularly vein leaving disc margin at about 3 o'clock.

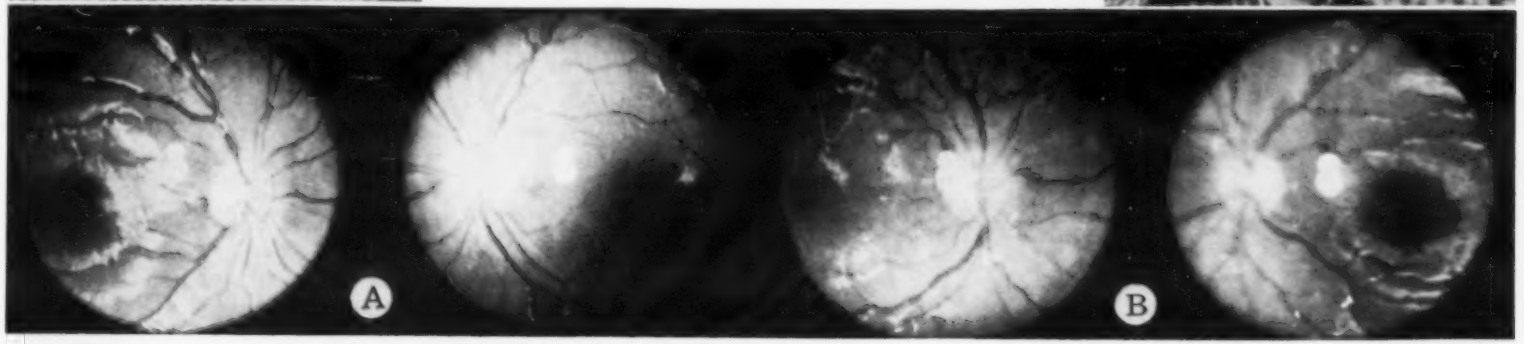


Fig. 2 (Pair 2).—D. S. (*A*), and J. S. (*B*), identical twins, 6½ years old.

1. Optic disc: All four eyes: large, slightly oval, with longer axis in vertical direction. Pronounced similarity.

2. Physiologic excavation: All four eyes: deep and wide. Pronounced similarity.

3. Disc margin: Peripapillary conus, more pronounced in *A* than in *B*. Slight pigmentary crescent in *A*, only indicated in *B*.

4. Pattern of vessels emerging from disc: All four eyes: separating well above surface of disc. Configuration similar.

5. First branching of arteries and veins: All four eyes: within limits of disc or conus.

6. Macula: All four eyes: small, deep dark. No central reflex.

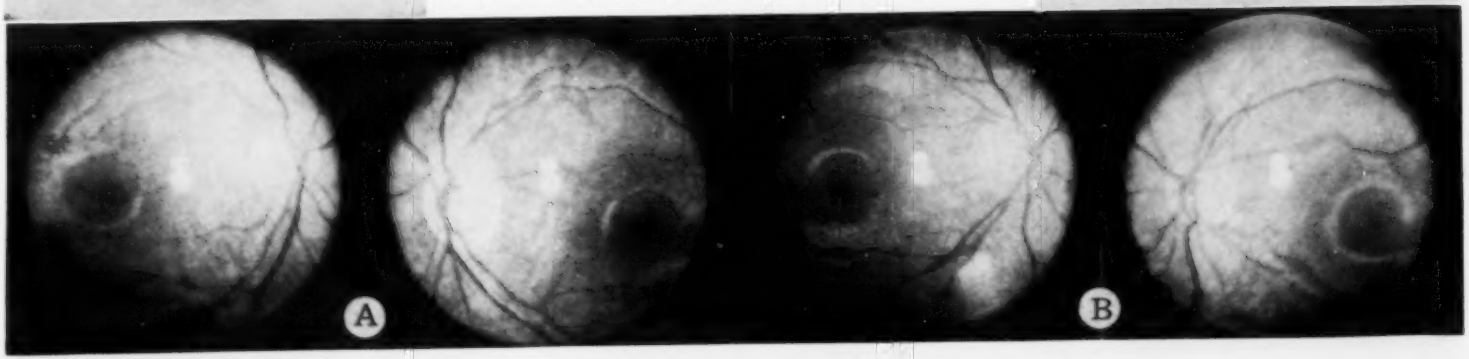
7. Perimacular area: All four eyes: grayish. Oval in *A*, right; circular in three other eyes.

8. Perimacular reflex: All four eyes: varying in extent and position; almost completely circular in *B*, left; extending temporally in both left eyes.

9. Fundus in general: All four eyes: light, almost albinotic type. Choroidal markings prominent.

10. Reflexes: All four eyes: minimal, due to light-colored fundus.

11. Retinal vessels: All four eyes: dissimilar.



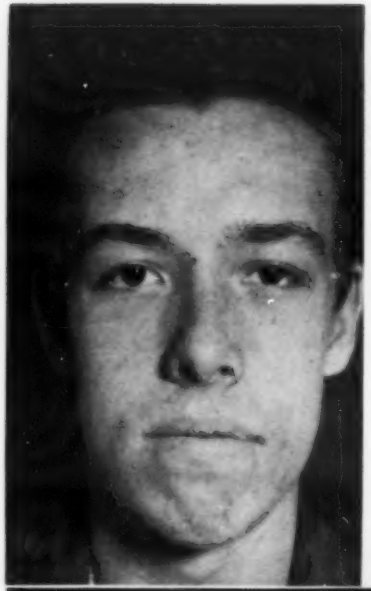


Fig. 3 (Pair 3).—A. S. (*A*), and D. S. (*B*), identical twins, 16 years old.

1. Optic disc: All four eyes: small, round.

2. Physiologic excavation: All four eyes: shallow.

3. Disc margin: All four eyes: no remarkable similarities.

4. Pattern of vessels emerging from disc: All four eyes: separating just above surface of disc. In both eyes of *A*, and in *B*, right: V-shaped pattern of veins with acute angle toward temporal side; nothing comparable in *B*, left.

5. First branching of arteries and veins: All four eyes: within disc or at its margin.

6. Macula: Both eyes of *A*: gray and indistinct; both eyes of *B*: dark and circular. All four eyes: minute central macular reflex.

7. Perimacular area: All four eyes: gray and circular.

8. Perimacular reflex: All four eyes: small reflex crescent along upper border of perimacular area. In addition, in *B*, right: extensive reflex band below perimacular area, extending in temporal direction.

9. Fundus in general: All four eyes: medium-light-colored fundus. Few choroidal markings visible.

10. Reflexes: All four eyes: few, irregularly scattered.

11. Retinal vessels: All four eyes: dissimilar. In *B*, right, artery below macula very tortuous; nothing comparable in any other eye.

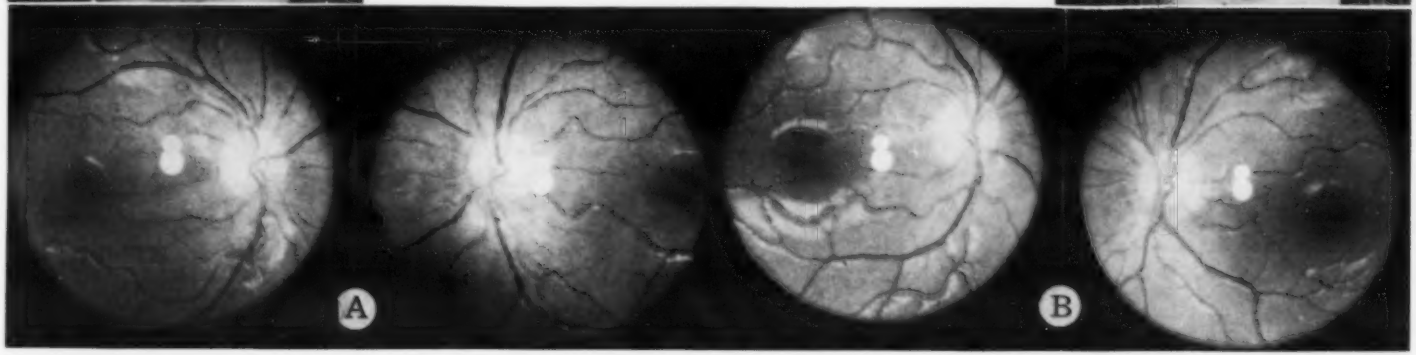


Fig. 4 (Pair 4).—R. P. (*A*), and P. P. (*B*), identical twins, 19 years old.

1. Optic disc: In *A*, right, and *B*, left; small, round; in *A*, left, and *B*, right: larger, oval.

2. Physiologic excavation: In *A*, right; shallow and narrow; in *A*, left, and *B*, right: moderately deep and wide; in *B*, left: moderately deep and small.

3. Disc margin: In *B*, left: pigmentary crescent along temporal margin; nothing comparable in any other eye.

4. Pattern of vessels emerging from disc: In *A*, right: well above surface of disc; in three other eyes: just below surface of disc.

5. First branching of arteries and veins: All four eyes: within disc or at its margin.

6. Macula: All four eyes: dark and circular; in *A*, right, and both eyes of *B*: small; in *A*, left: considerably larger. Central reflex faintly indicated in both eyes of *A*; minute in both eyes of *B*.

7. Perimacular area: In *A*, right: medium gray, with ill-defined limits; in *A*, left: dark, with well-defined limits; in both eyes of *B*: light, not circumscribed.

8. Perimacular reflex: In both right eyes: small reflex at upper nasal margin; in *A*, left: large reflex at upper and lower margins; in *B*, left: small reflex at upper margin, larger one below.

9. Fundus in general: In *A*, medium-dark fundus, without choroidal markings; in *B*, medium-light fundus, choroidal markings faintly indicated. All four eyes: Below, disc area of irregularity in shape of triangle with apex toward disc, and swerving temporally. In both eyes of *A* it is marked only by striations and increased reflexes; in the two eyes of *B* there are, in addition, pigmentary changes.

10. Reflexes: All four eyes: scattered; in *A*, right, and *B*, left: moderately pronounced; in *A*, left: very pronounced; in *B*, right: faint.

11. Retinal vessels: In both eyes of *A*, and in *B*, right: crowding of vessels at upper nasal margin of disc; nothing comparable in *B*, left. In *A*, right, and *B*, left: characteristic branching of inferior temporal vein. In *A*, left: increased tortuosity, particularly of arteries below the macula. There are differences in the arteriovenous ratio between *A* and *B*.

Fig. 5 (Pair 5).—M. F. (*A*), and J. W. (*B*), identical twins, 63 years old.

1. Optic disc: All four eyes: of medium size, round.

2. Physiologic excavation: In both eyes of *A*, and in *B*, left: shallow; in *B*, right: deep. In both eyes of *A*: narrow; in both eyes of *B*: wide.

3. Disc margin: In *A*, right: small scleral crescent; in *A*, left, and both eyes of *B*: small scleral ring. In both eyes of *A*: faint pigmentary crescent, nasally.

4. Pattern of vessels emerging from disc: In *A*: just above surface of disc; in *B*, right: well above surface of disc; in *B*, left: just below surface of disc.

5. First branching of arteries and veins: In *A*: within disc or at its margins; in *B*: within disc.

6. Macula: In both eyes of *A*, and in *B*, right: senile macular changes compatible with physiologic aging; in *B*, left: early senile macular degeneration.

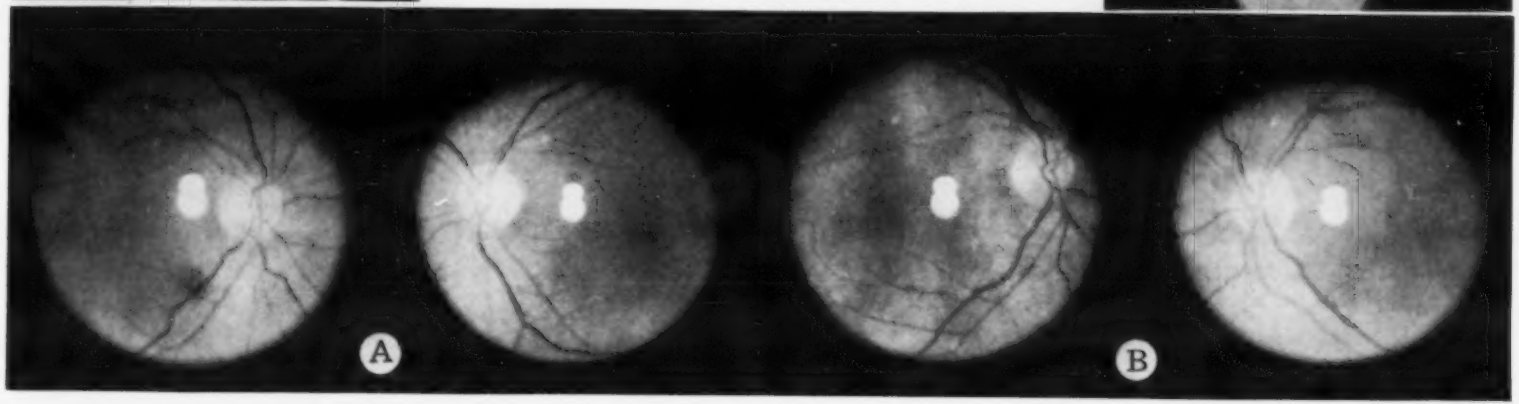
7. Perimacular area: In *A*, right: indistinct; in *A*, left, and *B*, right: barely indicated; in *B*, left: early senile degeneration. In all four eyes vessels can be followed up to well within perimacular area.

8. Perimacular reflex: All four eyes: absent, as to be expected in aged subjects.

9. Fundus in general: All four eyes: light, dull, with slight changes compatible with physiologic aging. In *A*, right, hemorrhagic area, deep to inferior temporal vein; nothing comparable in any other eye.

10. Reflexes: All four eyes: absent, as is to be expected in aged subjects.

11. Retinal vessels: Both left eyes: slight similarity in arrangement of vessels on nasal side of disc; less marked in both right eyes.



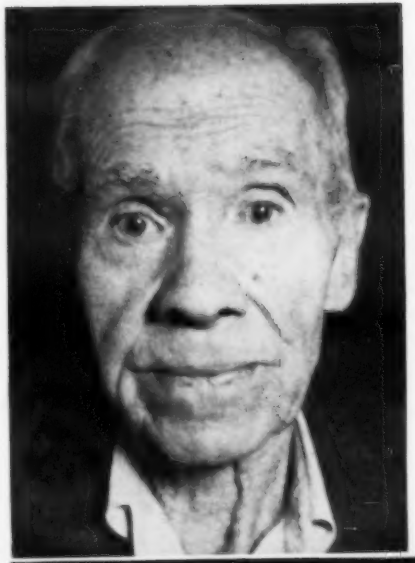


Fig. 6. (Pair 6).—B. B. (*A*), and A. B. (*B*), identical twins, 82 years old.

1. Optic disc: All four eyes: oval, with longer axis in vertical direction, tilted nasally.

2. Physiologic excavation: All four eyes: deep.

3. Disc margin: All four eyes: senile peripapillary atrophy, least pronounced in *B*, right.

4. Pattern of vessels emerging from disc: In *A*: just above surface of disc; in *B*: just below surface of disc.

5. First branching of arteries and veins: In *A*, right: within scleral ring; in *A*, left: within disc or scleral ring; in *B*: within disc area.

6. Macula: In *A*, right, and in both eyes of *B*: indistinct, due to senile changes; in *A*, left: ill-defined, dark gray.

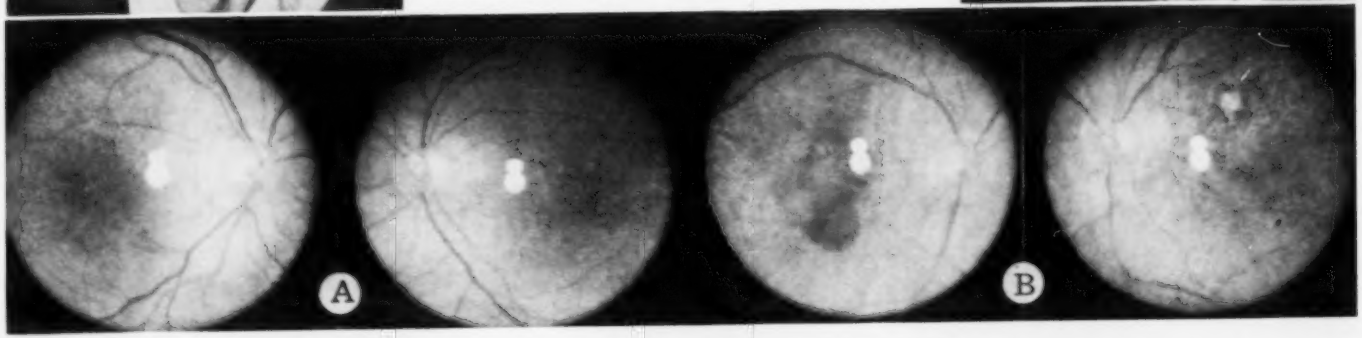
7. Perimacular area: In *A*, right: scattered pigmentary or hemorrhagic disturbances; in *A*, left: indistinct, vessels entering perimacular area. In *B*, right: indistinct with large hemorrhagic area below macula; in *B*, left: degenerative changes, with large area of pigmentary atrophy above and nasally.

8. Perimacular reflex: All four eyes: absent, as is to be expected in senile subjects.

9. Fundus in general: All four eyes: light. In *A*: minimal degree of choroidal sclerosis; in *B*: marked choroidal sclerosis.

10. Reflexes: All four eyes: absent, as is to be expected in senile subjects.

11. Retinal vessels: in *A*: arteriovenous ratio slightly increased; terminal vessels quite distinct. In *B*: arteriovenous ratio markedly increased; terminal vessels indistinct.



dissimilarity. Even the most conscientious attempt at an objective evaluation can lead only to tentative conclusions.

FINDINGS

Optic Disc.—The optic disc and its immediate surroundings have been studied under five different headings. In the first place, size and shape of the optic disc were carefully noted. In four pairs of identical twins there was striking similarity, amounting almost to identity. In another pair (Fig. 1) the corresponding sides showed marked similarity, while in a last pair (Fig. 4) cross symmetry was encountered.

Physiologic Excavation.—Next, depth and width of the physiologic excavation were recorded. Again, striking similarity, bordering on identity, was present in the eyes of four pairs of twins. In one pair (Fig. 4) there was more or less pronounced cross symmetry. In another pair (Fig. 5) the resemblance between the two eyes of each individual twin was greater than that between one twin and the other; this difference is probably due to varying stages of aging in these two subjects.

Disc Margin.—Only in one pair of twins was a pigmentary crescent observed in all four eyes, but even here it was more pronounced in one twin than in the other (Fig. 2). The same applies with regard to congenital peripapillary conus, also encountered in this pair of little girls. The two pairs of aged twins showed peripapillary atrophy, but not to a strikingly similar degree.

Pattern of Vessels Emerging from Disc.—The level at which the retinal vessels emerge from the disc was the same in all four eyes of two pairs of twins (Figs. 2 and 3); in the other four pairs there was a less pronounced degree of correspondence, or no similarity whatsoever. Only in the pair of little girls (Fig. 2) was the pattern formed by the vessels emerging from the disc strikingly similar in all four eyes.

First Branching of Arteries and Veins.—As the place of first branching of the retinal arteries and veins is either within or closely related to the disc area, it was studied together with other data pertaining to the papilla. In three pairs of twins the location was identical or similar in all eyes. In the other pairs the correspondence was restricted to three eyes, or to both sides of one twin.

When the findings relative to the optic disc and its immediate surroundings are summarized, it becomes obvious that there are varying degrees of correspondence. It is most marked with regard to size and shape of the optic disc, as well as depth and width of the physiologic excavation. Somewhat less marked is the similarity in the level at which the retinal vessels emerge, and the place of their first branching.

Macula; Perimacular Area; Perimacular Reflexes.—In observations of the posterior pole the following features were noted: size and color of the macula, as well as the central reflex; color and shape of the perimacular area, and perimacular reflexes. The two pairs of children showed pronounced similarity in color and shape of the macula; in the adolescent group the similarities were less marked, while in the aged twins intervening physiologic and pathologic processes made observations unreliable. With regard to the perimacular area, the highest degree of similarity was encountered in the male adolescent pair (Fig. 3). The little boys (Fig. 1) presented marked cross symmetry. One of the female adolescent twins (Fig. 4*B*) showed similarity approaching identity of the perimacular areas in the two fundi, but no resemblance to either of those of the other twin. In the four younger pairs the perimacular reflexes were in part surprisingly similar. Sometimes there was a pattern of cross symmetry, as in Pair 1; or there were only minor variations, as in Pair 2. The little girls (Fig. 2), however, showed in both left eyes a characteristic extension of the perimacular reflex in the temporal direction. The two other pairs combined striking similarities with characteristic differences of certain details.

Altogether, the similarities in the central region of identical twins are remarkable

They are, however, less pronounced than those of the optic disc and its immediate surroundings, and it appears that they are more closely related to the age of the subject at time of observation.

Fundus in General.—For the retina as a whole, comparison is on much safer ground, as there exists an accepted scale of fundus types. The over-all appearance seemed identical in five of the pairs of monozygotic twins. The only exception was the pair of adolescent girls, where the eyeground of Subject B was lighter than that of Subject A; but all four eyes presented characteristic findings of a triangular area of aplasia below the disc and corresponding to the site of a coloboma, which, however, again varied from the one subject to the other (Fig. 4). In the two pairs of aged twins, there were marked differences of pathologic involvement, in spite of the identical over-all impression of the fundi: Only in the right eye of Subject A of Pair 5 was a hemorrhagic spot noted. The degenerative changes in Subject B of Pair 6 were much more advanced than those in his fellow twin.

Fundus Reflexes.—These are, of course, absent in aged twins; yet even in the younger pairs the similarity in this respect was not very striking. The resemblance was most pronounced in the four eyes of the adolescent boys (Fig. 3), while in Pair 4 the reflexes were markedly different, in keeping with other discrepancies between the fundi of these twins.

Retinal Vessels.—With regard to the retinal vessels the observations permit no generalizing statement. On the one hand, slight, or even sometimes striking, similarities were noted. For instance, the angle formed by the secondary branches of the superior temporal vein in the right eye of Subject A, Pair 1, showed a fair degree of cross symmetry with the corresponding branches in the left fundus of Subject B. There was some similarity between the right eyes of the twins, particularly the vein leaving the disc margin at about 3 o'clock (Fig. 1). The closest resemblance of vascular arrangement was found in the left fundi of the subjects of Pair 5: The patterns of crowded vessels leaving the disc in the upper nasal quadrant were almost identical. Yet, while such similarities in course and arrangement of the retinal vessels are impressive, many characteristic features remain without counterpart. For example, in the right eye of Twin B, Pair 3, there was tortuosity, approaching beading, along the course of the inferior macular artery; nothing even faintly comparable appeared in any of the other three fundi of this pair. Another unmatched finding was the pattern of the vessels in the temporal half of the left fundus of Twin A, Pair 4. This absence of a corresponding feature was considered all the more significant as the crowded pattern of the vessels above the disc was quite similar in both eyes of Twin A, and in the right eye of Twin B, of the same pair.

It stands to reason that different factors must be responsible for the many similarities of vascular pattern close to the optic disc, in contrast to the lack of correspondence in the further course of the retinal vessels.

Summary.—The foregoing report of findings in six pairs of monozygotic twins demonstrates that none of them are similar in all points examined. The extent of similarity varies from one pair to the next, and it is of interest to note that even in the pair which presents identity or similarity in all other aspects (Fig. 2) no marked resemblances are encountered in course and distribution of the retinal vessels.

It may be no more than coincidence that in the right eye of one of the twins presented by Vogelsang[35] there was also a temporal extension of the perimacular reflex, quite similar to those observed in both left fundi of twins of Pair 2 of the present series. Furthermore, mention should be made of the suggestion of congenital colobomas of the choroid, which, though varying slightly in appearance, are encountered in all four eyes of twin Pair 4.

COMMENT

In general, the findings in the present small series of identical twins confirm earlier observations. The highest degree of correlation obtains for the impression of the fundus as a whole; slightly less marked is the correspondence with regard to size, color, shape, and physiologic excavation of the papilla; the pattern of the vessels at the disc shows conformity as often as dissimilarity, entirely in keeping with the statement of Waardenburg.[38]

Earlier observers paid less attention to corresponding features in the macular area of identical twins. No other portion of the fundus undergoes more pronounced changes throughout the lifetime of the individual; but after due allowance has been made for this fact, the extent of similarities in monozygotic twins is surprising.

Findings in the present series confirm the prevailing opinion that, in spite of occasionally prominent similarities of detail, the vascular tree of identical twins presents few common features.

This lack of correspondence has been most extensively discussed by Stern.[31] Starting out from earlier observations concerning the far-reaching correspondence of capillary patterns in monozygotic twins,[21] Stern tried to demonstrate the same type of similarity in the retinal arteries. As this attempt was unsuccessful, he proposed an interesting theory: With regard to hereditary determination, there exists a difference between the ectodermal and the mesodermal portions of the eyeground; the parts derived from neuroectoderm include the optic nerve and the retina, with its pigment epithelium, while the blood vessels originate from associated proximal mesoderm.* Stern concludes that while in twins the parts of the ocular fundus derived from ectoderm are inclined to show identity, the incidental correspondences in the course of the retinal arteries are not directly due to hereditary factors; such similarities are ascribed to a preformed ectodermal anlage, which, in turn, provides formative stimuli for the mesodermal elements.

The assumption that occasional similarities in the vascular arrangement of the retinal vessels in twins are due to a preformed ectodermal anlage can probably be traced to the original work of Newman.[23] From observations in armadillos, he developed the theory that twinning is initiated and carried out in the ectoderm, with endoderm and mesoderm becoming involved only passively, and considerably later. On that basis, Newman explained mirror imaging and situs inversus viscerum. But it is hardly necessary to take recourse to this theory in order to account for the lack of correspondence in the retinal vascular tree of monozygotic twins, and another interpretation may be suggested.

An essential weakness of Stern's approach to the problem is that he expected the similarities in the capillary patterns of other body regions to be duplicated in the retinal arteries. However, through the ophthalmoscope we see mainly arterioles and venules, while the precapillaries and capillaries cannot be clearly observed. An ingenious method for the study of the fine macular vessels has been proposed by Ballantyne.[2] More definitive findings may be possible as a result of further refinements of biomicroscopic technique. In any case, nothing can be gained by comparing portions of the vascular system which are not homologous.

While the capillary pattern of the retina cannot be directly observed through the ophthalmoscope, indirect information is gained by a study of the macular and perimacular areas in twins. The foveola is a zone of avascularity in which even capillaries are absent.[32] Changes in the vascular arrangement of the macular and perimacular regions are accompanied by modifications of the ophthalmoscopic appearance of the posterior pole.[32] The extent of the retinal vessels can therefore be approximately estimated on the basis of ophthalmoscopic observations.

In this context, it is of importance to note that in identical twins the macular area often

* Mann,[18] p. 17.

presents a high degree of similarity with regard to size, color, and reflexes; a lower degree of correlation obtains for the perimacular region. This finding permits the conclusion that the vascular arrangement at the posterior pole shows a marked degree of correspondence. A still higher degree of correspondence in the arrangement of the retinal vessels in identical twins has generally been reported at or near their point of emergence from the optic papilla. In contrast, the course of the retinal vessels in all other portions of the fundus shows few, if any, similarities.

Provided we are permitted to interpret the appearance of the macular and perimacular areas as indirectly indicative of the vascular pattern in the central region, we find that no single statement will cover the behavior of the retinal vessels in identical twins along their entire course. It is necessary to distinguish three different zones within the vascular tree as a whole—the region at or close to the papilla, the region surrounding the macula, and, finally, the course of the vessels in the rest of the retina. Once such a division is made, we find that in the axial fundus (the region around the disc), as well as at the posterior pole (the region around the macula), the retinal vascular tree of identical twins shows much greater similarities than in the rest of the fundus. It is in this remaining third that pronounced similarities are lacking, or only incidentally present, and it must be attempted to explain this observation.

The similarities of the retinal vessels of identical twins at or near the papilla are probably due to the close relationship of mesodermal and ectodermal structures in that region. The similarities in the macular and perimacular areas may find their explanation in the far-reaching correspondence of capillary arrangement in various body regions of identical twins. In microscopic examinations of nail beds, Schiller[30] found absolute concordance in the capillary patterns of all identical twins. Lehmann and Hartlieb[16] examined the capillaries in the lips, as well as those in the nail beds, and found an overwhelming degree of similarity among monozygotic twins, in contrast to the findings in heterozygotic twins of the same or different sex. It is true that examination of capillaries in one part of the body does not permit reliable conclusions as to their pattern in other body regions. Nevertheless, for the time being, and until it is proved or disproved by more detailed biomicroscopic studies, we may assume that similarities in the capillary pattern of identical twins account for the rather high degree of correspondence in the ophthalmoscopic appearance of the posterior pole. The range of discrepancies in the vascular pattern in other portions of the retina is evidently so much greater that a different explanation is required. Here the vessels are not of the order of capillaries, nor are they as closely related to ectodermal structures as at or near the papilla. On the other hand, the entire vascular system of identical twins shows so many corresponding features that the lack of similarity in the rest of the fundus seems all the more surprising. In passing, it may be mentioned that identical twins have the same blood groups, even the same subgroups, and type of agglutinogens[42]; the skin veins of homologous arms are in 75% of monozygotic twins of the same or essentially the same type[15]; the arterial system of the hands shows marked similarity[6]; blood pressure, pulse rate, and electrocardiogram present a high degree of correlation.[24]

A possible explanation of the differences in the course of the retinal vessels of identical twins may be attempted on an embryological basis. According to Mann,† the retina is completely avascular during the first period of its development. The central artery of the retina is just recognizable at 100 mm., i. e., the fourth month of intrauterine life. By the end of the fourth month a small area of the nerve fiber layer around the disc has been vascularized. The vessels begin to spread peripherally, but do not reach the ora serrata before the eight month. Only then is the vascular development of the retina completed.

† Mann,[18] p. 230.

It is true that the temporal branches are well established by the fifth month,‡ and that at the age of 6 months the retina is vascularized as far forward as a point just in front of the equator.§ The permanent vascular system of the retina takes shape over a period of months, and it is precisely during this time that differences between identical twins are most pronounced. On the strength of measurements of length and weight, Verschuer [34] arrived at the conclusion that the dissimilarities between uniovular twins are most marked about the middle of pregnancy and decline during the later part of intrauterine life. According to Verschuer, differences in development are mostly observed in the organs which participate in the circulation of blood, including the vessels. The period of the fifth month, during which the retinal vessels grow out from the region of the disc, is precisely the middle of pregnancy. Would it be too much to assume that differences in the life situation of identical twins, which seem to be most marked during this time, may result in changes or suppression of an identical anlage? Waardenburg [38] has shown that paratypical influences may lead to changes in the dimensions of the orbit of monozygotic twins. Walker [41] concluded that different plantar configurations in identical twins might be traceable to disturbances in the fetal growth of one of them during the critical period, in that case the third and fourth months. Finally, it might be remembered that the vascular arrangement of the retina may be looked upon as fluid from the point of view of phylogeny and comparative embryology, in contrast to other, more stable, regions of the eye.‖

Earlier observers found that in monozygotic twins the degree of correspondence varies in different parts of the fundus. The present study suggests that over and above this not even the retinal vascular tree should be examined as a whole, but that its various parts must be separately analyzed. Although a small series of cases like the present one does not by itself warrant far-reaching inferences,[28] the problem of the vascular tree in monozygotic twins seems worthy of further consideration.

‡ Mann,[19] p. 176.

§ Mann,[19] p. 215.

‖ Mann,[19] p. 11.

SUMMARY

The fundus oculi has been studied in six pairs of monozygotic twins. The findings of earlier observers, to the effect that the region of the papilla shows a high degree of correspondence, while the course of the retinal vessels presents few similarities, have been confirmed. However, it has also been established that the macula, as well as the perimacular region, exhibits a fair degree of correlation. On this basis it is concluded that the correspondence of retinal vessels in monozygotic twins varies in different parts of the vascular tree. While at or close to the papilla, and also in the macular and perimacular regions, there is extensive concordance, dissimilarity prevails in the other portions of the retinal vessels. This latter finding is explained on an embryologic basis and traced to influences during the critical period of development.

REFERENCES

1. Badtke, G.: Über einen Fall von spiegelbildlichem Einwärtsschielen bei eineiigen Zwillingen, Klin. Monatsbl. Augenh. **105**:231-237 (Aug.) 1940.

2. Ballantyne, A. J.: The Reflexes of the Fundus Oculi, Proc. Roy. Soc. Med. **34**:19-42 (Nov.) 1940.

3. Burns, R. A.: Hereditary Myopia in Identical Twins, Brit. J. Ophth. **33**:491-494 (Aug.) 1949.

4. Cockayne, E. A.: Transposition of the Viscera and Other Reversals of Symmetry in Monozygotic Twins, Biometrika **31**:287-294 (March) 1940.

5. Constans, G. M.: Unusual Eye Findings in Identical Twins, Am. J. Ophth. **27**:401-403 (April) 1944.

6. Danforth, C. H.: Comparison of the Hands of a Pair of Polydactyl Negro Twins, Am. J. Phys. Anthropol. **2**:147-165, 1919.

7. Fowler, E. P.: Studies of Deafness in Twins: Otosclerosis in Identical Twins, Laryngoscope **52**: 718-731 (Sept.) 1942.

8. Franceschetti, A., and Klein, D., in Amsler, M., and others, Editors: Lehrbuch der Augenheilkunde, Basel, S. Karger, 1948, p. 96.

9. Gates, R. R.: Human Genetics, New York, The Macmillan Company, 1946, Vol. I, p. 194.

10. Gesell, A., and Blake, E. M.: Twinning and Ocular Pathology, with a Report of Bilateral Macular Coloboma in Monozygotic Twins, Arch. Ophth. **15**:1050-1071 (June) 1936.

11. Glover, L. P.: Amblyopia in Identical Twins, Am. J. Ophth. **15**:140 (Feb.) 1932.

12. Hofmann, W. P., and Carey, E. T.: Congenital Myopic Astigmatism in Identical Twins, Am. J. Ophth. **25**:1495-1496 (Dec.) 1942.

13. Hofstetter, H. W., and Rife, D. C.: Miscellaneous Optometric Data on Twins, Am. J. Optom. **30**:139-150 (March) 1953.

14. Huber, A.: Ophthalmologische Untersuchungen an eineiigen und zweieiigen Zwillingen, Arch. Julius Klaus-Stiftg. Vererbgsforsch. **6**:41-122, 1931.

15. Kadanoff, D.: Untersuchungen über die Unterschiede in der Verästelung der Hautnerven und Venen der oberen Extremität bei ein- und zweieiigen Zwillingen, Ztschr. Morphol. u. Anthropol. **38**: 73-89, 1940.

16. Lehmann, W., and Hartlieb, J.: Capillaren bei Zwillingen, Ztschr. menschl. Vererb. u. Konstitutionslehre **21**:271-285, 1937.

17. Lehrfeld, L.: Homologous Twins Foretold by Eyegrounds, Eye, Ear, Nose & Throat Month. **27**:319-320 (July) 1948.

18. Mann, I. C.: The Development of the Human Eye, London, Cambridge University Press, 1928.

19. Mann, I. C.: Developmental Abnormalities of the Eye, London, Cambridge University Press, 1937.

20. Masters, S.: Strabismus in Twins, Am. J. Ophth. **35**:1825-1826 (Dec.) 1952.

21. Mayer-List, R., and Hübener, G.: Die Kapillarmikroskopie in ihrer Bedeutung zur Zwillingsforschung, München. med. Wchenschr. **72**:2185-2186 (Dec. 18) 1925.

22. Meyer-Schwickerath, G.: Zwillingsstatistische Untersuchung über den Einfluss von Umweltsfaktoren auf den Myopiegrad, von Graefes Arch. Ophth. **149**:695-700, 1949.

23. Newman, H. H.: The Biology of Twins (Mammals), Chicago, University of Chicago Press, 1917, p. 154.

24. Newman, H. H.: Multiple Human Births, New York, Doubleday, Doran & Company, Inc., 1940, p. 131.

25. Oberhoff, K.: Hyperopischer Astigmatismus und Hyperopie bei eineiigen Zwillingen, Klin. Monatsbl. Augenh. **107**:577-580, 1941.

26. Orth, H.: Extreme Diskordanz der Refraktionswerte eineiiger Zwillinge, Klin. Monatsbl. Augenh. **124**:304-306, 1954.

27. Pillat, A.: Zur "Ähnlichkeitsdiagnose" der Augenmerkmale bei eineiigen Zwillingen und über "Spiegelbildsymmetrie" gewisser Merkmale, Ztschr. Augenh. **71**:35-47, 1930.

28. Price, B.: Primary Biases in Twin Studies, Am. J. Human Genet. **2**:293-352 (Dec.) 1950.

29. Rychener, R. O.: Identical Twins with Hyperopia, Amblyopia ex Anopsia, and Colloid Deposits in Optic Discs, Am. J. Ophth. **14**:685-686 (July) 1931.

30. Schiller, M.: Zwillingsprobleme, dargestellt auf Grund von Untersuchungen an Stuttgarter Zwillingen, Ztschr. menschl. Vererb. u. Konstitutionslehre **20**:284-337, 1936.

31. Stern, H. J.: Vergleichende Untersuchungen des Augenhintergrundes bei Zwillingen, Klin. Monatsbl. Augenh. **90**:215-222, 1933.

32. Tower, P.: Differential Diagnosis of Common Diseases of the Eyeground, New York, Grune & Stratton, Inc., 1953, p. 151.

33. Tower, P.: Observations on Hole in the Macula, New York, S. Karger, 1954, pp. 28-29.

34. von Verschuer, O.: Die vererbungsbiologische Zwillingsforschung, Ergebn. inn. Med. u. Kinderh. **31**:35-120, 1927.

35. Vogelsang, K.: Makulakolobom bei eineiigen Zwillingen, Klin. Monatsbl. Augenh. **98**:322-327, 1937.

36. Vogt, A.: Die senile Determination des Keimplasmas, beobachtet an eineiigen Zwillingen, Schweiz. Med. Wchnschr. **65**:576-579 (June 22) 1935.

37. Vogt, A.; Wagner, H.; Richner, H., and Meyer, G.: Das Senium bei eineiigen und zweieiigen Zwillingen, Arch. Julius Klaus-Stiftg. Vererbgsforsch. **14**:475-597, 1939.

38. Waardenburg, P. J.: Refraktion und Zwillingsforschung, Klin. Monatsbl. Augenh. **84**:593-637, 1930.

39. Waardenburg, P. J.: in Sorsby, A., Editor: Modern Trends in Ophthalmology, New York, Paul B. Hoeber, Inc., 1947, Vol. II, pp. 169-187.

40. Waardenburg, P. J.: Twin Research in Ophthalmology, Docum. ophth. **4**:154-199, 1950.

41. Walker, N. F.: Discordant Monozygotic Twins with Retinablastoma and Cleft Palate, Am. J. Human Genet. **2**:375-384 (Dec.) 1950.

42. Wiener, A. S.: Blood Groups and Transfusion, ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1948, p. 196.

Coats' Disease

A Clinical and Pathologic Study

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Difficulties in the clinical diagnosis of the eyes of two children with unilateral complete retrolental membranes, later studied pathologically, have stimulated this report. Both eyes were enucleated because of the possibility of a tumor, but histologic examination demonstrated the lesions to have been the result of massive subretinal hemorrhage with partial organization.

A number of conditions other than retinoblastoma must be considered in the differential diagnosis of eyes with clinical evidence of a retrolental membrane or of a progressively enlarging retinal or subretinal mass. The term "pseudoglioma" has frequently been used to describe this group of diseases, the specific diagnosis of which is often possible only after histologic study. Even then, in advanced stages the findings may be inconclusive. A number of excellent reviews on this subject have appeared in the recent literature.* Those diseases which are usually included under the name "pseudoglioma" follow.

1. Congenital anomalies:

   (*a*) Retinal aplasia and dysplasia: This condition is characterized by maldevelopment of the retina and incomplete development of secondary vitreous with associated dysplasia of the central nervous system.

   (*b*) Persistent hyperplastic primary vitreous: This disease, involving the eyes of infants, has recently been studied and clarified by Reese.† This anomaly also is usually unilateral.

2. Retrolental fibroplasia: A great deal has appeared in the recent literature on this disease. It almost always shows bilateral changes and occurs only in premature infants.

3. Organization of a vitreous mass following inflammation or hemorrhage: The clinical diagnosis is often difficult and there may be no history of either injury or systemic infection.

4. Inflammatory retinal detachment: This may be produced, for example, by a choroidal tubercle. Inflammatory signs elsewhere in the eye may be helpful in the diagnosis.

5. Tumors other than retinoblastoma: These may include diktyoma, or angiomatosis retinae.

6. Exudative retinitis of Coats: This is characterized by transudation of edema fluid into and beneath the retina. It is often called serofibrinous degenerative retinitis of Leber.

7. Coats' disease: A symptom complex in which retinal, or subretinal, connective tissue plaques are the result of hemorrhage from various sources. It is sometimes called external hemorrhagic retinitis of Coats.

Both the eyes included in this report presented this problem in differential diagnosis.

REPORT OF CASES

CASE 1.—A. S., a 15-year-old girl, was first seen on Feb. 12, 1954, complaining that the left eye had been blind and divergent for the past six months. She was otherwise in good health. Although there was no history of recent injury, the left eye had been struck four years previously by the branch of a tree, without apparent damage.

At the time of her first examination, there was no light perception in the left eye, and visual acuity in the right eye was 6/6. The anterior chamber, O. S., was shallow, and a network of new vessels could be seen on the surface of the iris. Behind the clear lens was a grayish-yellow mem-

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* References 1 to 3.

† Reese, A. B.: Persistent Hyperplastic Primary Vitreous. The Edward Jackson Memorial Lecture given at the annual meeting of the American Academy of Ophthalmology, New York, Sept. 21, 1954.

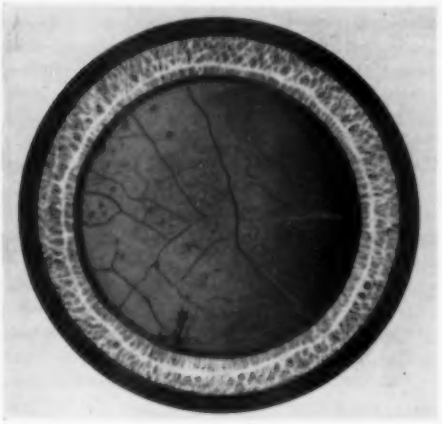


Fig. 1 (Case 1).—Vascularized retrolental membrane.

Fig. 2 (Case 1).—Whole mount of the sectioned globe, showing organized and partially necrotic subretinal hemorrhage and more recent subretinal hemorrhage, causing complete retinal separation. Reduced to ⅗ of mag. × 4.5.

brane, over the surface of which were many blood vessels terminating in small hemorrhages and aneurysmal dilatations (Fig. 1). Intraocular pressure was 30 mm. Hg (Schiøtz). Examination of the right eye was entirely negative. Because the left eye was already blind, with impending glaucoma, and because of the possibility of tumor, enucleation was advised.

Gross Description.—The globe measured 23 by 23 by 22 mm. The cornea was clear, and the eye could be transilluminated faintly. A small posterior synechia was found in the 7 o'clock position. Horizontal calottes were made. The retina was completely detached (Fig. 2) and rested against the posterior surface of the lens, where it was held by a greenish gelatinous material which almost completely filled the subretinal space. On the temporal side of the globe, the subretinal space was occupied by a light-tan, firm, irregular mass, approximately 2 mm. thick. Adjacent to this larger lesion were many small granular particles, apparently composed of the same material.

Fig. 3 (Case 1).—High-power view, showing necrotic remains of old subretinal hemorrhage, cholesterol-crystal clefts, and acute inflammatory reaction to the necrosis. Reduced to about ⅗ of mag. × 88.

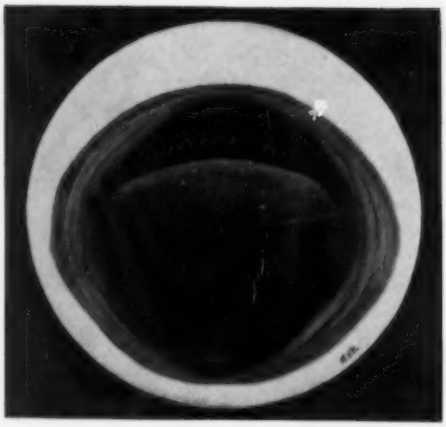


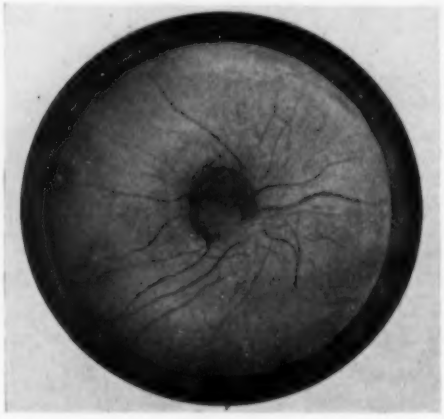
Fig. 4 (Case 2).—Eye viewed from an angle, showing ectropion uveae and forward displacement of the iris.

Microscopic Description.—The cornea was normal. The iris was adherent to the more peripheral portions of the functioning trabeculum, resulting in a partial closure of the filtration angle. Over the anterior surface of the iris, a few new vessels could be recognized, and the pigment epithelium of the iris was drawn slightly forward to produce an early ectropion. Scattered throughout the choroid were chronic inflammatory cells, heavily concentrated in a few small areas. Large irregular plaques and mounds of fibrous connective tissue seemed to arise from breaks in Bruch's membrane. These were richly vascularized in their peripheral layers, but were less so in portions more distant from the choroid. Strands of proliferated pigment epithelial cells were scattered within these connective tissue areas. Within the plaques were many long cholesterol-crystal clefts, frequently surrounded by foreign body giant cells. In some areas, connective tissue had effectively isolated large necrotic remnants of hemorrhage (Fig. 3). Many partially necrotic polymorphonuclear leucocytes were present in some of these areas. In one of the connective tissue plaques new bone was beginning to form.

The retina was completely detached. On one side of the section it lay folded against and fused with the subretinal organized connective tissue, already described. In such areas the retinal architecture was markedly distorted, and many large, fluid-filled cysts were found within the retina. On the other side of the sections the retina was pressed forward against the posterior surface of the lens by a homogeneous eosinophilic coagulum, containing scattered red blood cells and foamy macrophages. There was loss of the rod and cone layer and slight distortion of the outer nuclear and molecular layers. A few hyaline exudates were seen in the outer nuclear layer and many new vessels in the nerve fiber layer behind the lens.

Fig. 6 (Case 2).—Whole mount of sectioned globe, showing complete separation of the retina, a large retinal cyst, and vascularized connective tissue behind the lens. Reduced to ⅝ of mag. × 45.

Fig. 5 (Case 2).—Retrolental membrane vascularized from a central depression.



Case 2.—E. B., a 16-month old Negro girl, was first examined at the Children's Hospital of Philadelphia at the age of 9 months. She had been admitted with a diagnosis of subdural hematoma, and examination of the eyes had revealed massive preretinal hemorrhages in both eyes. Her subdural hemorrhages were aspirated, and a complete recovery was effected. Her fundi were not reexamined, however, until seven months later, when

she was referred to the eye clinic because of changes noted in the left pupil. External examination at this time revealed an extensive ectropion uveae (Fig. 4). The iris was drawn forward away from the lens, and a complete retrolental membrane was visible, with large vessels radiating outward from a central depression (Fig. 5). X-rays showed no evidence of calcification within the eye. Enucleation was recommended because of the possibility of tumor.

Gross Description.—The globe measured 22 by 22 by 24 mm. The cornea was clear. The pupil was elongated in the horizontal direction, and the pigment epithelium extended for some distance over the anterior surface of the iris. The eye could not be transilluminated. Sections made horizontally revealed a complete separation of the retina (Fig. 6). The subretinal space was filled with coagulated blood and pale-gray serum.

Microscopic Description.—The cornea was normal, but the filtration angle was nearly obliterated by peripheral anterior synechiae. Along the anterior surface of the iris was a thin fibrovascular membrane, which appeared to draw the pigment epithelium forward over the pupillary border, producing a marked ectropion uveae.

The ciliary body and choroid were normal. There were slight proliferation and separation of pigment epithelium in a few areas. The retina was completely detached and was trapped behind the lens by a cone-shaped mass of young fibrovascular connective tissue. The retina showed marked distortion of its architecture and a few large cysts. In its outer layers were hemorrhages in various stages of organization. One large vessel within the retinal stalk contained an organized and partially recanalized thrombus. The subretinal space was filled with blood and serum. Large numbers of small congested blood vessels were found within the optic nerve.

COMMENT

Although the various forms of pseudoglioma may be indistinguishable on the basis of clinical, or even histologic, observation, it seems probable that these two eyes should be included in the poorly defined symptom complex known as Coats' disease.

In his original paper,[4] Coats described a group of eyes, most of them from otherwise healthy young males, in which massive white or yellow subretinal exudates were observed ophthalmoscopically. These exudates had a characteristic histologic appearance and were thought by Coats to be the result of organizing retinal and subretinal hemorrhages. He later suggested the name "external hemorrhagic retinitis" for this condition. Leber,[5] in 1915, on the basis of independent histologic studies, suggested that the lesions were inflammatory and that the hemorrhages were of secondary importance. It has since been demonstrated,‡ however, that the disease he described, and which is now called "external exudative retinitis," or "serofibrinous degenerative retinitis of Leber," is a separate entity characterized by the accumulation of edema fluid and bladder cells within and beneath the retina. External hemorrhagic retinitis of Coats, on the other hand, is now considered by most authors to be a symptom complex, the result of organization of subretinal hemorrhages from a number of causes. Wilder,[8] for example, has shown that an identical histologic picture may be the result of hemorrhage due to infection with nematode larvae. A similar condition may occur in elderly people, possibly as a result of hemorrhage from sclerotic choroidal vessels in the macular region. Reese[9] has described organization of intraretinal and subretinal hemorrhages in the eyes of newborn infants and has named the condition massive retinal fibrosis. Elwyn,[10] on the other hand, does not believe that all these conditions should be included and would prefer to retain the name Coats' disease for a specific entity in which the subretinal hemorrhages are the result of a congenital vascular malformation.

The first eye in the present report has an appearance histologically very similar to that which Coats described as external hemorrhagic retinitis. Review of a large number of sections failed to reveal any specific source for the hemorrhage, and no definite etiology could be determined. Although there are scattered signs of inflammation, they appear to be secondary to necrosis rather than a response to an infectious agent. The more fully organized areas of hemorrhage are apparently of some duration, but the presence of fresh blood beneath the retina indicates a more recent secondary hemorrhage with subsequent complete separation of the retina.

‡ References 1, 6, and 7.

Trauma must be considered as a possible cause of the original hemorrhage.

In the second eye, it seems probable that retinal and preretinal hemorrhage, associated with subdural hematomas, resulted in the formation of vascular occlusions and subretinal plaques of connective tissue. Several months later, massive subretinal hemorrhage secondary to these circulatory disturbances produced the complete separation of the retina seen clinically as a retrolental membrane.

SUMMARY

Two eyes enucleated because of suspicion of tumor are presented in which the retrolental mass was found to be a result of retinal separation due to subretinal hemorrhage.

In one eye the hemorrhage probably was the result of vascular changes associated with a subdural hematoma, while in the other no specific etiologic factor could be found.

These eyes are presented as examples of the poorly defined entity known as Coats' disease.

Dr. Harold G. Scheie gave permission to use the material in Case 1 and assisted in preparation of this manuscript.

REFERENCES

1. Sanders, T. E.: Pseudoglioma: A Clinicopathologic Study of 15 Cases, Am. J. Ophth. **35**: 199-212 (Feb.) 1952.

2. Heath, P.: Massive Separation of the Retina in Full Term Infants and Juveniles, J. A. M. A. **144**:1148-1154 (Dec.) 1950.

3. Wetzel, J. O.: Pseudoglioma of the Retina, Am. J. Ophth. **24**:164-173 (Feb.) 1941.

4. Coats, G.: Forms of Retinal Disease with Massive Exudation, Roy. Lond. Ophth. Hosp. Rep. **17**:440-525, 1907-1908.

5. Leber, T.: Die Retinitis exsudativa (Coats), Retinitis und Chorioretinitis serofibrinosa degenerans, in Graefe, O., and Saemisch, T.: Handbuch der gesamten Augenheilkunde, Leipzig, W. Engelmann, 1915, Vol. 7, Pt. 2, p. 1267.

6. Lamb, H. D.: Exudative Retinitis, Am. J. Ophth. **21**:618-641 (June) 1938.

7. Marshall, J., and Michaelson, I. C.: Exudative Retinitis in Childhood, Tr. Ophth. Soc. U. Kingdom **53**:102-118, 1933.

8. Wilder, H. C.: Nematode Endophthalmitis, Tr. Am. Acad. Ophth. **54**:99-109, 1950.

9. Reese, A. B.: Massive Retinal Fibrosis in Children, Am. J. Ophth. **19**:576-582, 1936.

10. Elwyn, H.: The Place of Coats's Disease Among the Diseases of the Retina, Arch. Ophth. **23**:507-521, 1940.

Facility of Flow Through the Trabecular Meshwork

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This report presents one further detail in the investigation of factors which are responsible for the resistance to outflow of aqueous humor from the eye. One portion of this study which has already been reported was concerned with tonographic determination of facility and rate of outflow of aqueous humor in patients*; another portion has been experimental, concerned with measurement of facility of outflow from enucleated eyes, both normal and glaucomatous.†

It has been shown that the facility of outflow from enucleated eyes differs by only about 10% from that found in vivo by tonography.[4] Furthermore, the external two-thirds of the perilimbal sclera, with its included portions of the outflow channels, can be removed from enucleated normal human eyes without appreciably increasing the facility of outflow.[5] It has appeared from these findings that the principal anatomic resistance to flow is to be found in the immediate neighborhood of Schlemm's canal. In glaucomatous eyes the resistance may, of course, be differently distributed.

In attempting to locate the site of resistance more precisely, the present investigation has been aimed at evaluating the resistance of the corneoscleral meshwork. This has also been the aim of investigations carried out by Perkins.[6] He has compared the pressure in Schlemm's canal with the anterior chamber pressure in monkeys, and has determined the influence of exteriorizing Schlemm's canal on the resistance to outflow. His results have indicated that the corneoscleral meshwork may normally offer a very low resistance to flow. However, in these experiments it was not perfectly certain that the meshwork had escaped injury during dissection of the sclera or cannulation of Schlemm's canal. In the present investigation a somewhat different technique has been utilized for evaluating the resistance of the meshwork. In this work a portion of the trabecular meshwork has been removed and the influence on facility of outflow has been determined.

METHOD

The facility of outflow from enucleated normal human eyes before and after goniotomy was determined by means of a capillary flowmeter and electronic strain gauge in a manner described in an earlier report.[4] The measuring apparatus was connected to the eye by means of flexible polyethylene tubing and a 20-gauge needle, which was inserted through the cornea near the limbus. Insertion of the needle was facilitated by making a preliminary tiny incision with the point of a knife part way through the stroma. After insertion through the cornea the point of the needle was advanced across the anterior chamber slightly beyond the opposite pupillary border and there was made to pick up the edge of the iris in order to establish free communication between the anterior and the posterior chamber. This was done to insure equal pressures on the two sides of the iris and to prevent the unnatural deepening of the anterior chamber which

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Normal enucleated eyes were supplied for this study by the Boston Eye Bank.

From the Howe Laboratory of Ophthalmology, Harvard Medical School, and Massachusetts Eye and Ear Infirmary.

This investigation was supported by Research Grant B-218 of the Institute of Neurological Diseases and Blindness of the National Institutes of Health, U. S. Public Health Service. Purchase of part of the apparatus was financed by the Alfred P. Sloan Foundation.

*References 1, 2, and 3.

†References 4 and 5.

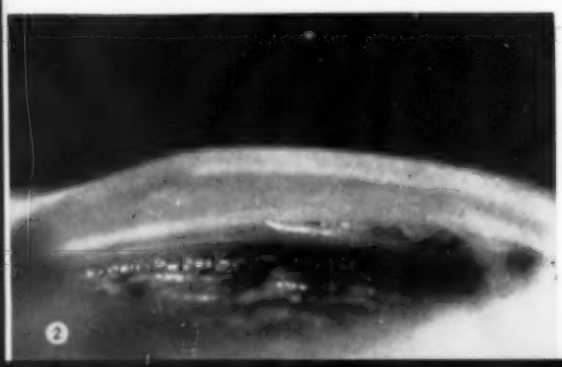
Fig. 1.—Direct view of the normal angle of the anterior chamber of a human eye after removal of a portion of the cornea. This shows Schwalbe's line and the trabecular meshwork with a band of pigment in front of Schlemm's canal, as well as the scleral spur and ciliary band.

usually results if fluid is injected solely into this chamber.

The facility of outflow was determined by permitting 0.9% sodium chloride solution to flow continuously from the capillary flowmeter into the eye, so that the intraocular pressure gradually attained a level at which the rate of outflow equaled the rate of inflow. The establishment of this steady state was signaled by a leveling off of the pressure in the eye to a constant value, and this was made evident by means of a continuous graphic recording of the pressure by a recording potentiometer. Under the conditions employed in these studies, the steady state was usually achieved at a pressure of 20-25 mm. (mercury). From the rate of flow in the steady state and the corresponding intraocular pressure the facility of outflow was then calculated. The facility of outflow, which is the reciprocal of resistance to outflow, provides a particularly convenient quantitative expression for the rate (in cubic millimeters per minute) at which aqueous humor can escape from the eye in proportion to each millimeter (mercury) of intraocular pressure. This coefficient has been calculated for enucleated eyes from the following equation:

$$\text{Coefficient of Facility of Outflow} = \frac{\text{Rate of Flow at Steady State}}{\text{Intraocular Pressure at Steady State}}$$

Fig. 2.—View of the angle of the anterior chamber comparable to Figure 1, but showing in one-half of the angle the disruption of the trabecular meshwork, which was accomplished by curetting with a transcorneal needle. This is one of the eyes in which no change in outflow was found, but a similar picture was found in all eyes which had goniotomy.



The resistance to flow offered by the corneoscleral meshwork was evaluated by comparing the facility of outflow before and after removal of the meshwork over a quarter to a third of the circumference. Removal of the meshwork was accomplished by curettage with the tip of the transcorneal needle. The procedure was initially carried out under gonioscopic control, but soon it was found to be as easily performed by utilizing a frontal view without gonioscopy. The curettage was performed employing the broadest aspect of the point of the needle so as to avoid sharp incision. The needle was swung in an arc with the site of corneal transfixion as a fulcrum, in the same manner as in clinical goniotomy. The tubing which connected the needle to the strain gauge was sufficiently flexible to permit this operation, and, despite the manipulation, the cornea maintained a good seal about the needle. In control experiments, in which the same maneuvers were carried out without the needle touching the trabecular meshwork, the manipulation itself was without detectable influence on the facility of outflow.

What was accomplished by curettage was evaluated by microscopic examination, as well as by measurement of outflow. Fluorescein was added to the perfusion fluid after completion of the measurements, and the course of the flow of fluid from the eye was examined by observing the appearance of fluorescent material at the surface of the eye with a low-power microscope. This observation served to establish, among other things, that no appreciable leakage occurred about the transcorneal needle. After this procedure, the eyes were fixed in 4% solution of formaldehyde U. S. P. A disc 6 to 8 mm. in diameter was then cut from the center of the cornea, and the angle of the anterior chamber was examined directly with the slit-lamp biomicroscope. The eyes were next embedded in paraffin, sectioned, stained, and examined microscopically. The cross sections were cut at regular intervals through the curetted quadrant in each eye. The normal angle on the other side of the chamber was included in each section for comparison.

RESULTS

The average value for facility of outflow in enucleated human eyes was a little greater than the average value obtained in normal patients by tonography. The average for enucleated eyes of both this and a previously published study[4] was 0.287 (corrected for 37 C), whereas the average tonographic value, corrected for rise in episcleral venous back-pressure during tonography according to Linner's observations,[7] is 0.252 cu. mm.

per minute per millimeter of intraocular pressure.

The values for facility of outflow before and after curetting away of the trabecular meshwork over a quarter to a third of the circumference in 19 enucleated, presumably normal, human eyes are presented in the Table. In 12 of these eyes the facility of outflow was not significantly altered; in 6 it was definitely increased, and in 1 it was slightly decreased. In the eyes in which the facility of outflow was unaltered it was observed that the outflow of fluorescein from the anterior chamber to the episcleral surface was approximately the same in curetted and in uncuretted quadrants, but in some of the eyes in which the facility of outflow was increased the fluorescein appeared to flow out principally in the curetted quadrant. By subsequent gonioscopy, after removal of a central disc of cornea, the trabeculae in all cases appeared to have been torn apart and partially torn away, as illustrated in Figures 2 and 3. An opening through to the scleral wall was evident in each case, although in most instances shreds or sheets of the meshwork remained attached at Schwalbe's line and at the scleral spur. Microscopic examination of sections of the angle confirmed that the trabecular meshwork between the anterior chamber and Schlemm's canal had been torn open, as illustrated in Figure 4, in at least a quarter of the circumference in all of the eyes. It was further evident microscopically that not only was the trabecular meshwork open, but, also, the outer wall of Schlemm's canal was somewhat damaged. Unfortunately, no conclusive difference could be discerned microscopically between the eyes in which curettage had increased the facility of outflow and those in which the outflow had not been affected.

*Influence of Goniotomy on Facility of Outflow**

No Change	Increase	Decrease
0.38 → 0.37	0.41 → 0.52	0.39 → 0.31
0.20 → 0.20	0.32 → 0.57	
0.17 → 0.16	0.15 → 0.56	
0.31 → 0.31	0.17 → 0.49	
0.09 → 0.09	0.27 → 0.58	
0.22 → 0.22	0.11 → 0.32	
0.27 → 0.27		
0.31 → 0.30		
0.14 → 0.14		
0.17 → 0.20		
0.36 → 0.36		
0.29 → 0.23		

* In 19 enucleated normal human eyes, at 25 C.

Fig. 3.—A view similar to Figure 2, showing an open furrow plowed between Schwalbe's line and the scleral spur by curettage of the trabecular meshwork.

COMMENT

The finding that the trabecular meshwork could in some eyes be torn away over a quarter to a third of the circumference of the angle of the anterior chamber without necessarily altering the facility of outflow indicates that in these eyes no appreciable resistance to outflow was offered by the meshwork, and that the resistance must have been located principally in the intrascleral portions of the outflow channels. It seems unlikely that any loss of resistance from opening the trabecular meshwork was exactly compensated in 12 out of 19 eyes by an equal increase in resistance elsewhere. Furthermore, the detritus from curettage of the meshwork apparently had little tendency to obstruct the outlets from Schlemm's canal, since an actual decrease in facility of outflow was found in

Fig. 4.—Typical cross section of the angle after curettage, showing the scleral spur remaining but the trabecular meshwork torn away. The anterior chamber has been opened into what was formerly Schlemm's canal.

only one eye. On the other hand, the increase in facility of outflow which was found in six eyes after curettage suggests that in these eyes the curettage may have accomplished something in addition to opening the trabecular meshwork. The indeterminate amount of damage to the scleral wall of Schlemm's canal which was observed in microscopic sections suggests that collector channels may also have been torn open in some eyes. It has been impossible to distinguish microscopically between eyes in which the facility of outflow was altered and those in which it was not. An alternate possible explanation for the difference in results of goniotomy in different eyes is that the meshwork may initially have had appreciable resistance to flow in some eyes and not in others. However, the facility of outflow was not significantly different in the two groups of eyes before the experiment, and there has been no other indication of initial dissimilarity.

The results so far obtained in these experiments are in essential agreement with those obtained by Perkins [6] employing different procedures. From both sets of experiments it appears that the trabecular meshwork of the angle of the anterior chamber offers little resistance to the outflow of intraocular fluid, but that the principal resistance is probably to be found in the immediate outlets from Schlemm's canal. Certain reservations must be acknowledged in coming to these conclusions; chief among these is the possibility that the resistance to outflow from enucleated eyes, such as those employed in these experiments, may differ in some fundamental aspect from that of normal eyes in vivo, even though quantitatively these resistances are not dissimilar. The results of experiments of the type described in this report would be more conclusive if the trabecular meshwork could be removed more discretely with no damage to the scleral wall of Schlemm's canal.

The distribution of resistance to outflow in glaucomatous eyes may well differ from what has been found for normal eyes. The resistance is known to be greater in glaucomatous eyes. Possibly by comparative measurements the site of the abnormality can eventually be determined.

REFERENCES

1. Grant, W. M.: Tonographic Method for Measuring the Facility and Rate of Aqueous Flow in Human Eyes, Arch. Ophth. **44**:204-214, 1950.

2. Grant, W. M.: Clinical Measurements of Aqueous Outflow, A. M. A. Arch. Ophth. **46**:113-131, 1951.

3. Grant, W. M., and Trotter, R. R.: Outflow of the Intraocular Fluid: Clinical Aspect, Council for International Organizations of Medical Sciences Symposium on Glaucoma, 1954, Oxford, Blackwell Scientific Publications, Ltd., to be published.

4. Grant, W. M., and Trotter, R. R.: Tonographic Measurements in Enucleated Eyes, A. M. A. Arch. Ophth. **53**:191-200, 1955.

5. Grant, W. M., and Trotter, R. R.: Factors Responsible for the Resistance to Outflow of the Intraocular Fluid, Proc. 17th International Congress of Ophthalmology, to be published.

6. Perkins, E. S.: Pressure in the Canal of Schlemm, Brit. J. Ophth. **39**:215-219, 1955.

7. Linner, E.: The Episcleral Venous Pressure During Tonography, Proc. 17th International Congress of Ophthalmology, to be published.

Radiation Studies on the Monkey Eye

I. Effects of Gamma Radiation on the Retina

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The effects of ionizing radiation on the crystalline lens have received intensive study in the past decade; however, radiation studies on the retina have not been emphasized.

In an earlier investigation Co^{60} gamma radiation was delivered to the head region of young adult monkeys. Pyknosis of the visual cells occurred with doses as low as 2000 r; however, no attempt was made to establish a time threshold for the appearance of retinal abnormalities.

It is the purpose of the present paper to describe the retinal changes found in a study of 48 monkeys which had been exposed to massive doses of Co^{60} gamma radiation delivered at a high dose rate. Our aim in this investigation was the determination of a time threshold for pyknosis of visual cells following a single dose of ionizing radiation, and also to ascertain whether this was a direct radiation effect. Fixed doses of 10,000 r were delivered either to the head (body shielded) (Group I), to the body (head shielded) (Group II), or to the entire body, including the head (Group III). Two animals from each group were then killed at specific intervals after irradiation. The ocular changes in each group were compared with the ocular conditions as they appeared in the eyes of five control animals subjected, except for radiation, to the same experimental conditions.

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From the Departments of Ophthalmology and Radiobiology, School of Aviation Medicine.

METHODS AND PROCEDURES

The animals used in this series of experiments were young adult male Macacus mulattus monkeys, divided into three subgroups, as indicated above. All animals were exposed to a Co^{60} gamma radiation source as described by Auxier,[1] and each animal received a total of 10,000 r at a rate of $1,000 \pm 50$ r/min. The animals were individually exposed in a horizontal position with the source located above.

The radiation field and dose rate were determined along the center line of the exposure cavity both in air and with a Masonite phantom in position. All measurements were checked with a high-range Co^{60} rate meter, a 2500 r Victoreen Thimble Chamber, $FeSO_4$, and one- and two-phase chemical dosimeters. In each of the three groups, the scatter component was measured, and necessary correction in exposure time was taken into consideration in the administration of the total dose of 10,000 r. During irradiation the animals were rotated around their longitudinal axis at a constant rate of 5 rpm.

The animals of Group I received localized head radiation. A lead collar 1½ in. thick was placed around the neck, thus shielding the body against radiation. About 5% scatter radiation to the thorax, and even less to the abdomen, was measured. The monkeys in the group receiving body irradiation again wore the lead collars around their necks to shield their heads from exposure. Similarly, 5% scatter to the eye region was measured under these conditions.*

Since the design of the exposure cavity would not permit uniform whole-body radiation to these relatively large monkeys, it was necessary in Group III to make two separate exposures with the shortest possible delay (one to two minutes) between irradiations. This was accomplished by combining the exposure arrangement for the Group I animals and the exposure arrangement for the Group II animals; that is to say, animals of Group III were first given approximately 10,000 r to the head with the lead collar shield in position. Immediately thereafter they were rotated into the same position as the Group II animals, and 10,000 r

* The irradiation procedure and dosimetry were directed by Mr. John Auxier, of the Radiobiological Laboratory of the University of Texas and the United States Air Force, Austin, Texas.

was delivered to the unirradiated remainder of the body with the lead collar shield still in place. In order to deliver the 10,000 r whole-body dose, it was necessary to take into account the scatter component and adjust the exposure time so that, as nearly as possible, constant total dose could be maintained. Control animals were treated identically except for irradiation.

In each group the animals were killed by decapitation at precisely 2, 4, 8, 12, 24, 48, 72, and 96 hours from the beginning of radiation exposure. Complete autopsies were performed on all animals. The eyes were enucleated immediately after decapitation, and the globes were transected just posterior to the ora serrata. The anterior portion was placed in Carnoy's solution and forwarded to Dr. von Sallmann's laboratory for evaluation of the effect on the mitotic activity of the lens epithelium. In previous studies,† von Sallmann found that ionizing radiation was able to arrest the mitotic activity of the lens epithelium in rabbits for a period of several days following irradiation. The posterior portion was placed in Zenker's solution. Immediately after decapitation, and prior to enucleation, tonometer readings were taken in animals surviving 48 hours and more.

Both eyes of all animals were dilated prior to irradiation with 2 drops of a 1% atropine solution, and were examined by ophthalmoscopy and slit-lamp biomicroscopy prior to, and several times daily after, irradiation.

In a few of the cases in which massive suspensions of blood corpuscles in the anterior chamber were observed biomicroscopically, chamber puncture and aspiration of aqueous humor were performed immediately after death. The cell number was counted as in routine blood analyses.

The retinae of some of the animals which had developed ophthalmoscopically visible papilledema, retinal edema, and retinal hemorrhages were also examined with a dissecting microscope immediately after the opening of the globes.

The two segments of the eye were embedded in paraffin and the sections stained with hematoxylin and eosin.

CLINICAL RESULTS

The clinical observations will be confined primarily to the head- and whole-body-irradiated animals (Groups I and III), since those receiving radiation to the body (head shielded) showed no reaction to radiation except for the presence of a very small number of cells visible in the anterior chamber at each examination. These either had disappeared completely or were seen to be adherent to the anterior lens capsule in animals surviving up to 96 hours. This cellular response in the anterior chambers of the head-shielded monkeys was understandable, since it is known that the eyes in these cases received about 5% (500 r) scatter even with the neck shielding. From other studies, it has been shown that 500 r of gamma radiation can cause a cellular reaction in the anterior chamber. There were no other eye changes noted in the head-shielded animals.

No clinically visible differences were noted between the eyes of those animals receiving whole-body radiation and those receiving head radiation with body shielded. Skin erythema was observed shortly after irradiation, but there was no nystagmus, epilation, conjunctival pigment proliferation, subconjunctival hemorrhages, or lens abnormalities during the observation period.

Several eye changes, however, were noted in both of these groups. Conjunctival vasodilatation was an early and constant finding. There was an outpouring of cells into the anterior chamber within the first 20 minutes after irradiation, followed later by progressive bulbar hypotony. Postmortem aspiration in five eyes yielded approximately 10,000 to 40,000 red cells and 3000 or less white blood cells per cubic millimeter. The clinically visible aqueous cells increased progressively throughout the first few hours and reached their maximum (several thousand free-floating cells) between 7 and 11 hours. A heavy and diffuse adherence of cells to the anterior lens capsule and the inferior half of the corneal endothelium was observed. Cellular elements in the retrolental space, especially equatorially, became apparent at about 48 hours and increased thereafter. A puffy, cloud-like change in the usually sharply defined vitreal elements was noted at about 90 hours in some animals; however, no change in fluidity was visible.

Retinal opacification was a prominent early finding, being noted first at about two and a half hours. This was invariably accompanied by an apparent color change in the retina, which became rather pale blue at 12 hours, and progressively increased in cloudiness to

† References 2 and 3.

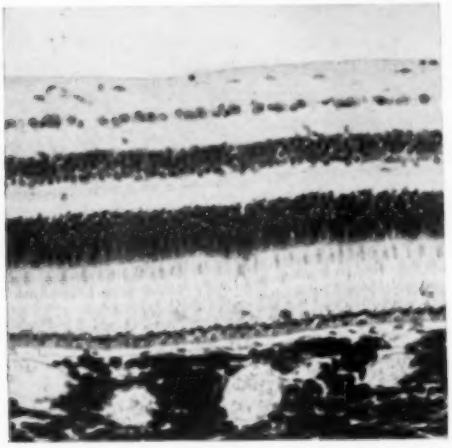


Fig. 1.—Normal appearance of retina of monkey 48 hours after exposure to 10,000 r of gamma radiation to body, head shielded. Zenker's fluid; hematoxylin and eosin; reduced to 76% of mag. × 265.

an almost gray-white appearance by 24 hours. This persisted or diminished slightly until the animal was killed. When the edema was well developed at the posterior pole, the macula appeared reddish-brown, as it appears in embolism of the central retinal artery.

Punctate hemorrhages or aneurysms, and, in some cases, flame-shaped hemorrhages, were seen in the retinae of 7 of the 32 head- and whole-body-irradiated monkeys, the majority occurring in those receiving radiation to the head only. Retinal hemorrhages were confined to the peripapillary and macular area. They appeared as early as two and a half hours after irradiation. It is emphasized that the animals were unanesthetized, and ophthalmoscopic examination was therefore hampered by the rapid searching eye movements which monkeys usually display. For this reason punctate retinal hemorrhages may well have been missed clinically. The retinae of animals surviving 48 hours or more were examined immediately after enucleation under a dissecting microscope, so that some confirmation of the clinically observed retinal edema, papilledema, and retinal hemorrhages was possible.

In animals surviving 48 hours and more, tactile tension and rather crude Schiøtz tonometer estimations were made, the latter only after decapitation. It was apparent that a severe ocular hypotony had set in sometime during the first 48 hours in the head- and whole-body-irradiated animals. Neither the 10 control eyes nor the eyes of the animals receiving radiation to the body exclusively showed a comparable drop in intraocular pressure.

Severity of Pyknosis of Rod Nuclei in Retina of Monkeys Correlated with Time Following Exposure to 10,000 r of Gamma Radiation *

Radiation to								
Group I Head (Body Shielded)			Group II Body (Head Shielded)			Group III Whole Body		
Animal No.	Time, Hr.	Severity†	Animal No.	Time, Hr.	Severity	Animal No.	Time, Hr.	Severity
317	2	1	342	2	0	30	2	1
323	2	1	321	2	0	243	2	1
319	4	3	281	4	0	26	4	3
384	4	2	316	4	0	27	4	3
315	8	4	319	8	0	28	8	4
318	8	4	314	8	0	23	8	4
383	12	4	392	12	0	385	12	4
382	12	4	313	12	0	387	12	4
338	24	4	320	24	0	312	24	4
347	24	4	344	24	0	431	24	4
183	48	4	244	48	0	256	48	4
242	48	3	276	48	0	405	48	4
273	72	4	270	72	0	43	72	4
31	72	4	50	72	0	160	43	4
247	96	2	343	96	0	25	96	4
352	52	4	193	96	0	194	90	4

* Animals 160 (43 hours) and 352 (52 hours) died accidentally of suffocation; all other animals were decapitated.
† 0 indicates no pyknosis; 1, 1% to 25% pyknosis; 2, 26% to 50% pyknosis; 3, 51% to 75% pyknosis, and 4, 76% to 100% pyknosis.

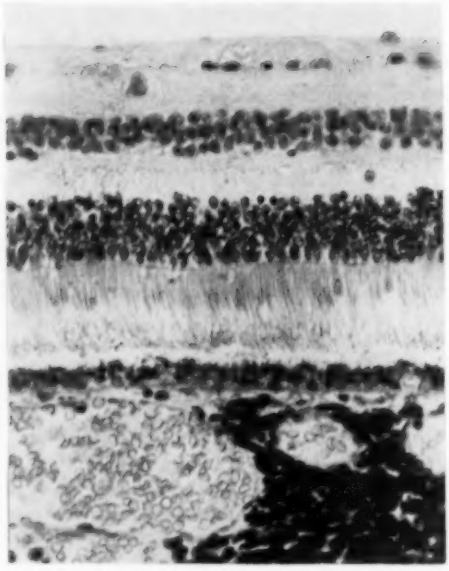


Fig. 2.—Pyknosis of a few rod nuclei in outer nuclear layer of monkey two hours following exposure of whole body (including head) to 10,000 r of gamma radiation. Zenker's fluid; hematoxylin and eosin; reduced to 76% of mag. × 480.

HISTOLOGICAL OBSERVATIONS

The radiation effects in conjunctiva, cornea, iris, and ciliary body consisted of edema, slight to moderate congestion of the vascular tissues, and moderate accumulation of red cells, polymorphonuclear leucocytes, and monocytes in the aqueous humor. Aggregations of cells were found in the trabecular meshwork associated with these conditions. The degree of severity of the inflammatory response increased slightly with time and reached its maximum at about 24 to 48 hours following irradiation; it then seemed to decrease gradually.

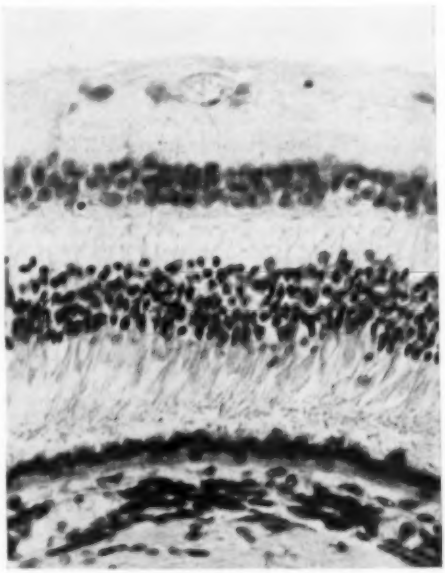
The vascular reactions in this experiment were considerably less than those observed in a survival study,[4] wherein similar (and also lower) doses of the same radiation were employed, but in which the animals died of radiation disease several days following exposure.

In the present study our interest was directed primarily to the effects of radiation upon the retina.

Histological evidence of retinal radiation effect was found only when the head was directly exposed (Groups I and III), and no retinal changes were observed in the animals whose heads were shielded (Table and Fig. 1).

The significant features of radiation damage to the retina were pyknosis of the rod nuclei associated with rod-cell cytoplasmic and extracellular edema. Pyknotic changes in the bipolar cells were occasionally seen but were observed only when advanced pyknosis had occurred in the outer nuclear layer. Subsequent autolysis and degenerative sequelae took place in the bacillary layer, external limiting membrane, and outer nuclear and outer plexiform layers. No histological evidence of radiation damage could be seen in the rod-free fovea centralis, indicating that cones are not so manifestly affected at this stage by this dose of radiation. This histo-

Fig. 3.—Pyknosis of about 75% of rod nuclei in outer nuclear layer of monkey four hours following whole-body exposure to 10,000 r of gamma radiation. Pyknosis is accompanied by cytoplasmic swelling and extracellular edema in outer retinal layers, distortion of external limiting membrane, and edematous swelling and beginning distortion of rod and cone members in bacillary layer. Zenker fluid; hematoxylin and eosin; reduced to 76% of mag. × 480.



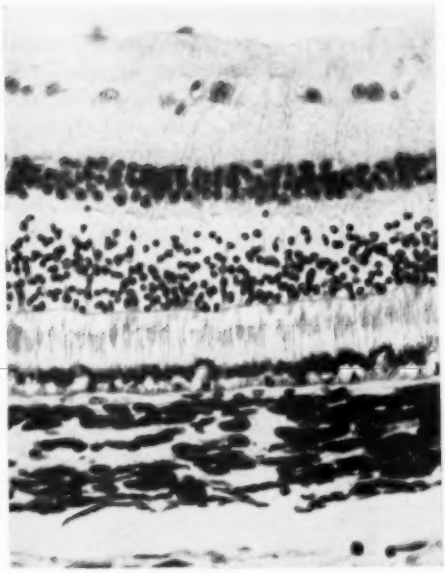


Fig. 4.—Complete pyknosis and beginning autolysis of rod nuclei in outer nuclear layer of monkey retina eight hours after whole-body exposure to 10,000 r of gamma radiation. Zenker fluid; hematoxylin and eosin; reduced to 76% of mag. × 1480.

Fig. 5.—Retina of monkey 12 hours after exposure of whole body to 10,000 r of gamma radiation, showing 100% pyknosis of rod nuclei, advanced edema of outer retinal layers, and destruction of bacillary layer, including cone members. Cone nuclei are distinguished by apparently normal chromatin structure but slightly elongated shape. Zenker fluid; hematoxylin and eosin; reduced to 76% of mag. × 430.

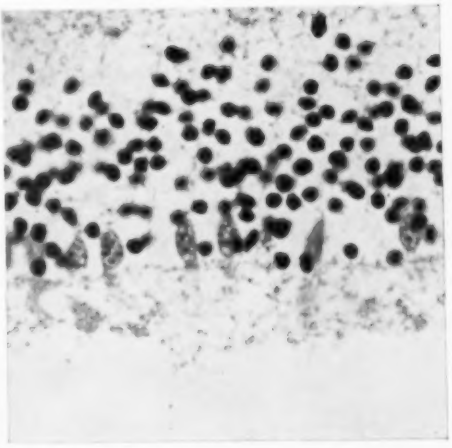
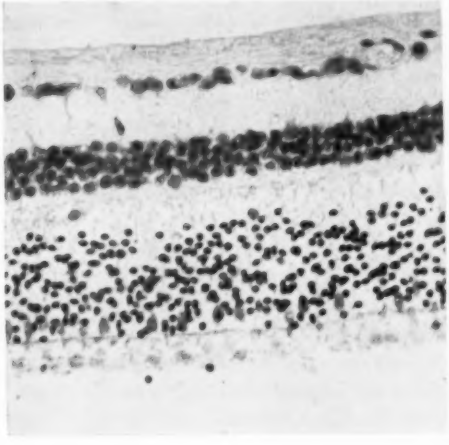


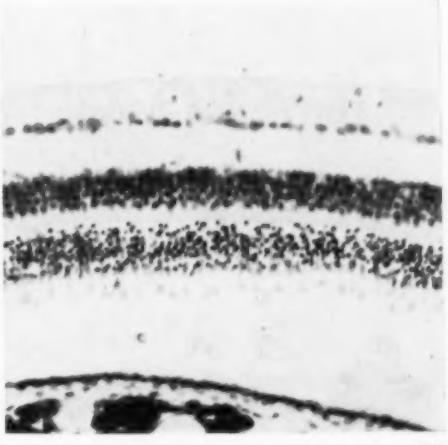
Fig. 6.—Higher magnification of portion of Figure 5. Fragmentation and decomposition of rod and cone members in bacillary layer. Zenker fluid; hematoxylin and eosin; reduced to 76% of mag. × 790.

logical finding confirms earlier studies ‡ and explains the clinical picture of a relatively normal fovea existing in the midst of an otherwise opaque retina. The earliest manifestation of pyknosis of the rod nuclei was

‡ References 5, 6, and 7.

Fig. 7.—Complete pyknosis of rod nuclei in retina of monkey 48 hours after whole-body exposure to 10,000 r of gamma radiation. Club-shaped deformation of cone members; fragmented outer limbs of rods and cones. Zenker fluid; hematoxylin and eosin; reduced to 76% of mag. × 295.





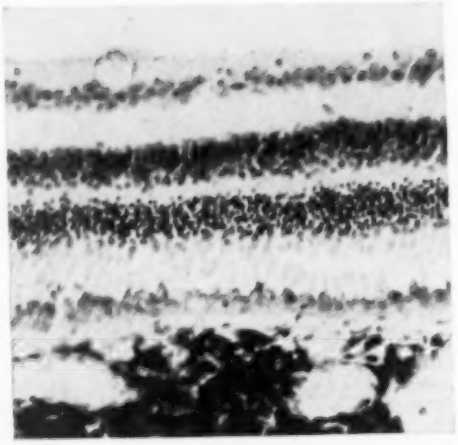


Fig. 8.—Retina of monkey 96 hours following exposure of entire body to 10,000 r of gamma radiation. Edema of pyknotic outer nuclear layer apparently regressing. Destruction of external limiting membrane and bacillary layer. Nuclear swelling in pigment epithelium. Choroid slightly congested. Zenker fluid; hematoxylin and eosin; reduced to 76% of mag. × 290.

noted in those animals killed two hours after irradiation (Fig. 2). At this time only a few rod nuclei, never more than about 10% of the whole rod-cell population, exhibited signs of hyperchromaticity and shrinkage, the latter indicated by a clear perinuclear zone. Four hours after irradiation, about 75% of the rod nuclei appeared pyknotic (Fig. 3). At eight hours, 100% pyknosis was usually found (Fig. 4). Our previous experiments, using x- or gamma rays, demonstrated that five to six hours was sufficient for the development of 100% pyknosis of the rod nuclei with doses of 4000 r or more.

Advanced pyknosis and autolytic changes seen in the present study were always accompanied by edema of the outer retinal layers, particularly of the outer nuclear layer. The edema progressed with time (Figs. 2 to 6) and reached its peak at about 24 to 48 hours. Later, it gradually regressed (Figs. 7 and 8). In the same animals F. S. Vogel observed a similar time pattern in the development and regression of meningitis. The radiation changes produced by head exposure (Fig. 9) did not differ significantly from those produced by whole-body irradiation. Our previous studies[4] revealed that 10 to 13 days

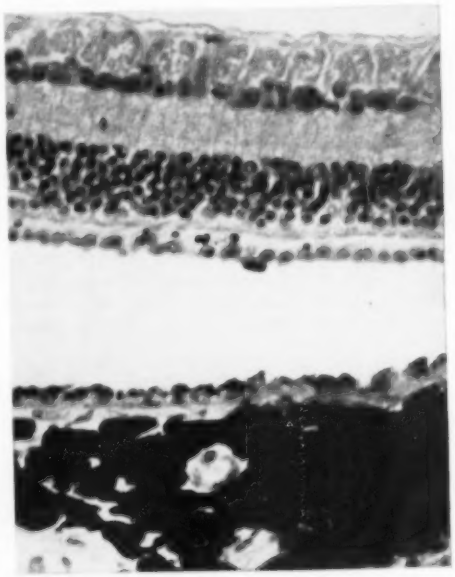
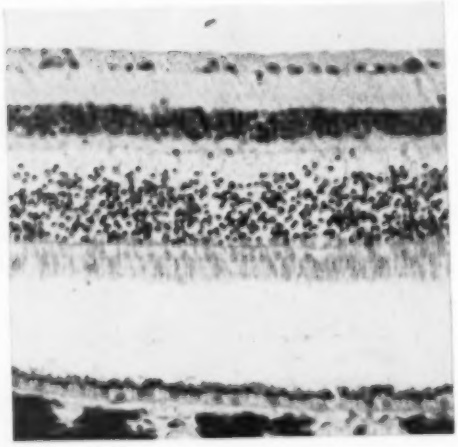


Fig. 10.—Retina of monkey 13 days after exposure to 6,000 r of gamma radiation to head. Advanced degeneration of outer nuclear layers. Only a few pyknotic rod nuclei and one row of apparently normal cone nuclei remain. Zenker fluid; hematoxylin and eosin; reduced to 76% of mag. × 400.

Fig. 9.—Retina of monkey 24 hours following exposure to 10,000 r of gamma radiation to head, body shielded. Advanced pyknosis of rod nuclei associated with edema of outer nuclear and bacillary layer. Zenker fluid; hematoxylin and eosin; reduced to 76% of mag. × 285.



after 6000 r to the head the retina appears markedly degenerated, with only a small band of cone nuclei remaining (Fig. 10).

As a matter of interest, there is one point which deserves special attention, namely, the excessive vulnerability of the retina, at least to mechanical trauma, which may lead to false conclusions. Thus, pyknotic rod nuclei were consistently present at the site of the cut made in transecting a normal globe just prior to immersion in the fixative. Here a significant number of rod nuclei were constantly found to be pyknotic and surrounded

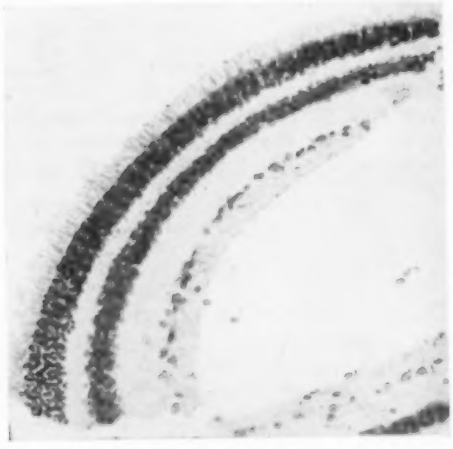


Fig. 11.—Retina of control animal, showing pyknosis of rod nuclei at break artificially introduced when globe was transected immediately after enucleation. Zenker fluid; hematoxylin and eosin; reduced to 76% of mag. × 230.

by a small clear zone (Fig. 11) in all 10 control eyes and in many irradiated eyes. These changes were evident even though the retinae were immediately immersed in fixative after the injury. The interpretation of these pyknotic changes produced in the retina by trauma after death is intriguing and requires further experimental study.

COMMENT

Following exposure of monkey eyes to 10,000 r gamma radiation, a prompt sequence of events occurs, characterized clinically by vascular disturbances and retinal opacification, and histologically by changes most marked in the outer layers of the retina. These were seen to be present at the earliest time of examination (2 hours) and were progressive during the 96 hours of observation, leading to evidence of complete degeneration in the rods and of their nuclei and to definite, but less severe, changes in the cones. Abnormalities were found only when the eyes were directly exposed to radiation, and not when the head region was protected.

These observations bear directly on the experiments of Cibis, Noell, and Eichel,[2] who found that the electroretinograms of various animals indicated a visual loss, primarily in rod function, after exposure of 3000 r of x-radiation or more to the eye. Such changes were demonstrable within 10 minutes following radiation.

While the experiments reported in this paper are concerned with only one dose level, it has been found in other studies that qualitatively similar changes occur in retinae exposed to dose levels as low as 2000 r. It has also been found that monkeys surviving irradiation for longer periods of time than here reported show complete disappearance of the bacillary layer, but with preferential persistence of the cone nuclei. Thus, 13 days after exposure to 6000 r gamma radiation to the head there is an extraordinary absence of rods and cones, and simply a single layer of cone nuclei in the region of the former outer nuclear layer.

SUMMARY

Co^{60} gamma radiation of 10,000 r was delivered at a rate of 1000 ± 50 r/min. to the head (body shielded) of 16 monkeys, to the body (head shielded) of a second group of 16 monkeys, and to the whole body (including head) of a third group of 16 monkeys. Five monkeys were employed as controls.

The animals were killed by decapitation at intervals of 2, 4, 8, 12, 24, 48, 72, and 96 hours following irradiation.

Ocular abnormalities were found in those animals who received radiation directly to the eyes.

Changes seen in the eyes of animals exposed to head radiation were essentially simi-

lar to those changes seen in the group receiving whole-body radiation. Clinical manifestations consisted of severe iridocyclitis, retinal edema, papilledema, severe hypotony, and, in a few cases, punctate and flame-shaped retinal hemorrhages.

Histological abnormalities consisted chiefly of pyknosis of the rod nuclei (apparent as early as two hours following irradiation), and degenerative sequelae in the outer nuclear and bacillary layers.

Both clinical and histological alterations developed in a definite time pattern.

Drs. F. S. Vogel, W. Haymaker, P. T. Shahan, and D. G. Cogan; Mr. J. Auxier; Master Sergeant J. Hughes, and Mr. I. W. Richardson gave assistance in this study.

REFERENCES

1. Auxier, J.: A High Level Co^{60} Facility, U. S. A. F. School of Aviation Medicine Report No. 55-40, to be published.

2. von Sallmann, L.: Report on Studies of the Effect of Roentgen Irradiation on the Rabbit Lens, US NRC, Declassified Document No. NYO-1508, April, 1950; abstracted, Nuclear Sc. Abst. **4**:631 (July 31) 1950.

3. von Sallmann, L.: Experimental Studies on Early Lens Changes After Roentgen Irradiation, A. M. A. Arch. Ophth. **45**:149 (Jan.) 1951.

4. Brown, D. V. L.; Cibis, P. A., and Pickering, J. E.: Ocular Lesions in Monkeys Following Massive Doses of Co^{60} Gamma Radiation to the Head, U. S. A. F. School of Aviation Medicine, Report No. 55-47, to be published.

5. Noell, W. K.; Eichel, B., and Cibis, P. A.: Visual Cells and Pigment Epithelium After High Intensity X-Radiation, Fed. Proc. **13**:106, 1954.

6. Brown, D. V. L.; Cibis, P. A., and Pickering, J. E.: Effects of High Doses of Mixed Neutron-Gamma Radiation on the Monkey Eye, U. S. A. F. School of Aviation Medicine Project Report, to be published.

7. Cibis, P. A.; Noell, W. K., and Eichel, B.: Ocular Effects Produced by High-Intensity X-Radiation, A. M. A. Arch. Ophth. **53**:651 (May) 1955.

Postnatal Development of Lamellar Cataracts in Premature Infants

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Lamellar cataracts are commonly thought to arise during gestation. Two cases, however, were reported by Guy[1] recently in which the opacities were observed to occur after birth. Two similar infants are here reported whose lenses were clear shortly after birth and who subsequently developed bilateral lamellar cataracts.

Bellows[2] states that Becker (1874), Jaeger (1881), Galezowski (1881), and others were of the opinion that lamellar cataracts developed prenatally, whereas von Graefe (1855), Panas, and Groenouw believed they appeared postnatally. Unilateral lamellar cataract has been observed in patients with keratitis (Becker, 1874) and after trauma (von Graefe, 1855-1857 and Law),[3] but none of these cases was proved not to have had the cataract prior to the disease or injury. Bellows also states that bilateral lamellar cataracts have been observed to develop in relation to tetany. Nevertheless, bilateral lamellar cataracts in the absence of tetany, local disease, or injury have been understood to have developed prenatally.

In the two cases reported here, there were no important medical complications during either mother's pregnancy, although the mother of Case 2 had mild toxemia for one week prior to the delivery. Both children received considerable oxygen therapy, but neither showed any evidence of retrolental fibroplasia. Medically, the postpartum course of these two babies was entirely without complications.

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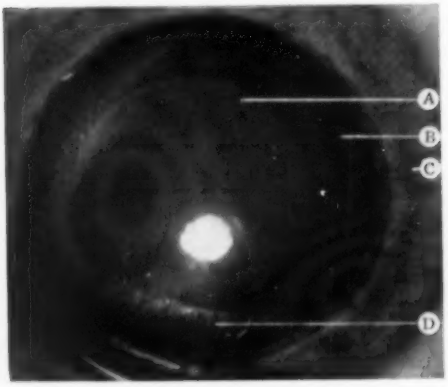
REPORT OF CASES

CASE 1.—M. K., a white female baby, was born in January, 1948, four weeks prematurely, and weighed 3 lb. 2 oz. (1417 gm.). I examined the baby when she was 2 weeks old, as part of a routine survey with reference to retrolental fibroplasia. The pupils were widely dilated with 1% atropine. The ocular media were perfectly clear. The discs and fundi were entirely normal. The patient was next seen at the age of 2 months. The parents thought that the vision had failed precipitously during the preceding three or four weeks, and their pediatrician was of the opinion that the child was blind. Examination at this time showed that the corneas were bright and clear; the anterior chambers were shallow; the pupils were 2 to 2.5 mm. in diameter and reacted to light. One could not obtain a red reflex from either fundus. The pupils were dilated with 1 drop of 2% atropine, after which typical lamellar cataracts were observed. A good red reflex could be seen all around the central nuclear opacity. The fundus details could not be visualized. On the following day, the child was again examined under ether anesthesia, and these findings were confirmed. The ocular tension was 22 mm. of mercury (Schiøtz) in each eye. On Aug. 4, 1948, a discission was performed on the right eye. After three days this discission appeared to be inadequate. On Aug. 7, a second discission was performed. The right lens became completely opaque, and absorption proceeded in the usual manner. Dilatation of the right pupil was maintained with 10% phenylephrine (Neo-Synephrine) and 0.25% atropine drops, which were instilled every four hours, day and night, for one week and every four hours thereafter until all of the cortical material had absorbed. On Oct. 22, 1948, the right fundus was examined and appeared to be normal. Retinoscopy indicated a retractive error of approximately +12 sph., and cataract glasses were prescribed. The child was then 9 months old. Owing to the formation of Elschnig pearl bodies, subsequent needlings were performed on the right eye on May 18, 1949, and Dec. 17, 1949; and, despite the diligent use of mydriatics, the pupils in both eyes have gradually become more

firmly attached to the underlying pupillary membrane. It was planned to defer surgery on the left eye until the child was 2 years of age, but when she reached 14 months of age, pendular nystagmus and a variable esotropia developed in this eye. Therefore, on May 18, 1949, a discission was performed on this eye. The resulting pupillary membrane in the left eye was needled on Sept. 23, 1951, and, despite the diligent use of mydriatics, both the pupils became increasingly difficult to dilate. The ocular tension has been repeatedly checked under ether anesthesia, however, and has always been found normal. The nystagmus became worse when either eye was occluded, and it was therefore very difficult to obtain an accurate measurement of the visual acuity, which has varied from 20/100 to 20/300 in the right eye and from 20/70 to 20/300 in the left eye. At near with glasses, her visual acuity was slightly better than 20/50 binocularly.



Right eye in Case 2.

A, lamellar cataract; *B*, zone of clear lens; *C*, iris; *D*, reflection of lids on cornea.

The patient, now aged 7, is attending regular school classes and is a most satisfactory student.

Case 2.—J. M., a white girl baby, was born March 31, 1952, weighing 3 lb. 2½ oz. (1432 gm.) at birth, about four weeks prematurely. Examination on this occasion showed that the ocular media were clear; there was no evidence of retrolental fibroplasia. The discs and retinal vessels were normal. The child was again examined on May 1, at 31 days of age. Examination at this time showed minimal dilatation of the peripheral retinal veins and elevation and edema of the peripheral retina. There were no hemorrhages. A reexamination was advised, but the child was not seen again until she was 18 months old, on Oct. 10, 1953, at which time the mother stated that two weeks previously she had noticed that "the left pupil was white." On examination it was found that there was a dense nuclear cataract in the left eye. The pupils were equal and reacted promptly to light. The corneas were clear; the anterior chambers were of normal depth. The pupils were dilated, and it was observed that there was a lamellar cataract in the right eye and an almost mature cataract in the left eye. The right fundus showed no abnormality. With the child under ether anesthesia, fundus examination was carried out at the Massachusetts Eye and Ear Infirmary on Oct. 25, 1953. The ocular tension was normal. One could barely obtain a dull red reflex through the periphery of the left lens. On Oct. 28, 1953, an extracapsular cataract extraction with full iridectomy was performed on the left eye. The postoperative course was uncomplicated, and the patient was discharged on Dec. 6. The dilatation of the left pupil was easily maintained with 0.2% scopolamine ointment. On Dec. 21, 1953, retinoscopy was performed and cataract glasses were prescribed (balance for the right eye and +11.00 D. sph. for the left). The child has worn glasses at least four hours every day without complaint. She was last examined on Oct. 12, 1954. The nuclear cataract in the right eye was slightly denser than it was when first observed, on Oct. 10, 1953, but the child appears to have useful vision in this eye. At the present time numerous Elschnig pearl bodies are forming in the pupil of the left eye, but there is still an adequate opening. This case has been followed for one and a half years.

COMMENT

The four cases now on record as having developed lamellar cataracts after birth were discovered as a result of the mass survey of premature infants with reference to the problem of retrolental fibroplasia. All four babies were premature, and all four received oxygen. It is possible that oxygen therapy may have been an "insult" to the immature lens, in the manner in which it is currently thought to be an insult to the vascularization of the retina. Routine periodic examinations of full-term infants might reveal other instances of lamellar cataracts developing after birth.

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REFERENCES

1. Guy, L. P.: Postnatal Cataracts in Premature Infants: Report of 2 Cases, Am. J. Ophth. **38**:65-68, 1954.

2. Bellows, J. G.: Cataract and Anomalies of the Lens, St. Louis, C. V. Mosby Company, 1944, pp. 255-308.

3. Law, F. W.: Unilateral Zonular Cataract, Brit. J. Ophth. **16**:385, 1932.

Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

AN EXCEPTIONAL LESION OF THE ORBIT

UNILATERAL exophthalmos is often a vexing problem in diagnosis in the minds of many ophthalmologists. Especially is this so when the causative lesion is an expanding, soft-tissue mass in which many of the helpful clinical and laboratory diagnostic criteria, such as positive x-ray evidence, pressure recession of the eyeball, a visible or palpable pulsation, or a bruit, may be lacking; in such cases biopsy is the only certain method of reaching a solution. In the case herein reported the diagnostic signs were comparatively definite but certain sequelae which followed surgery were uncommon.

REPORT OF CASE

In February, 1932, over 22½ years ago, I examined a 3-year-old girl and was told by her parents that the left eye had progressively and slowly been becoming more prominent during the previous three months; this prominence of the eye had not been accompanied by any other symptoms, although the parents suspected some loss of vision in this eye because of the child's tendency to turn her head to the extreme left when attempting to focus upon something in that area. There had been no history of trauma or previous disease which could be related to the presenting condition; the usual childhood diseases had been experienced without event. The family history was noncontributory, and there was no evidence of familial eye disease. Examination at the time revealed the vision in the left eye to be approximately 10/200; there were 6 mm. of exophthalmos in the left eye as measured with the Hertel exophthalmometer, and the eye diverged 20 arc degrees. Ocular motility was somewhat limited nasally but otherwise normal, and the texternal parts of the eyeball and the adnexa were normal. Pupillary reaction to light was sluggish. The media were clear, while the optic nerve head showed pallor and atrophy. The nerve head was clearly outlined, however, with no elevation or blurring. The retinal arteries were slightly attenuated, and the veins were moderately tortuous and overfilled; there were no retinal hemorrhages or exudates. The right eye was entirely normal both externally and internally. There was no evidence of a pulsation in the region of the left orbit, nor was there any bruit. No mass could be felt upon palpation of the area adjacent to the eyeball, and the globe could be forced backward into the orbit. X-rays taken in February, 1932, were reported as follows:

"There is a marked enlargement of the sphenoidal tissue on the left side and a slight generalized enlargement of the orbit. The optic canal measures 8 mm. in diameter on this side, whereas the canal on the right measures about 5 mm. The roof of the orbit is intact, and there is no involvement of any of the sinuses. This is consistent with the finding of an encapsulated new growth."

The diagnostic problem, then, seemed to be one involving a soft-tissue mass producing exophthalmos and atrophy of the optic nerve fibers, and it was felt that the lesion was probably a glioma of the optic nerve. Enucleation was done, with excision of several millimeters of the optic nerve; a glass-ball implant was placed in the orbit and a prosthetic eye inserted anterior to it. The patient made an uneventful convalescence from this operation.

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Presented, with additions, at a meeting of the New England Ophthalmological Society at Boston, Nov. 17, 1954.

After one or two postoperative visits in 1932, I did not see this patient again for a period of one year and three months, when she again presented herself for examination. At this time she was brought rather reluctantly by her parents because they had noticed that the prosthesis was becoming gradually more prominent and difficult to remove and insert. This condition had culminated in the extrusion of the glass-ball implant, which had occurred approximately 24 hours prior to this examination. Upon inspection of the socket, it was revealed that a slowly growing mass had been in the process of formation and now occupied the posterior two-thirds of the orbit; obviously, this was a probable recurrence of the original growth, and its removal was advised. Accordingly, in May, 1933, the patient was readmitted to the hospital, and operation was again performed; an orbital exenteration was performed, the lids being left intact. No intracranial surgery was done. After a period of convalescence the parents were advised to obtain an orbital prosthesis.

The later (final) pathologic diagnosis obtained from the Pathology Laboratory of the Massachusetts Eye and Ear Infirmary, and dated June 19, 1933, was reported as follows:

Recurrent glioma of optic nerve.

"Orbital tissue contains muscle, connective tissue, and free hemorrhage. No evidence of tumor found in celloidin sections, but a frozen section shows typical glioma of the optic nerve.

"Glioma of the optic nerve."

Although the parents of this girl were advised to have her return for postoperative check-ups in 1933, I did not see the patient again for 20 years and 9 months, when in March, 1954, she once again presented herself for examination; she was then 25 years of age. During this interval of years she had completed her schooling in the elementary and high schools, had taken secretarial training in business school, and was presently employed in an intown office, where she worked daily and apparently carried on her duties quite normally. She had not consulted any physician during this period, had apparently been in fairly normal physical condition, and had concealed the condition of her left eye by wearing a good-sized bandage, held in place with the usual black eye tie; she presented a most unusual lesion. Upon examination one could see a mass slightly smaller than a tennis ball protruding from the left orbit, which was covered by thin, markedly stretched, and parchment-like skin, through which appeared dark-bluish, tortuous, dilated veins. The thin, elongated lids contracted at intervals with the winking reflex, and there was a slit-like, elliptical opening, about 8 mm. in width and approximately 2 cm. in length, through which could be seen beefy-red tissue; the orbital mass was firm but not hard, was more

or less symmetrical, and extended approximately 1½ in. straight forward from the orbital rim; it had produced a uniform spreading of the orbital margins. Excision of this mass with the insertion of an orbital prosthesis was advised, but the patient's mother would not permit further operation.

This lesion represented a second recurrence in the orbit of the original glioma of the optic nerve, the tumor having been slowly increasing in size during this period of 20 years; during this long interval it obviously had not incapacitated the patient's normal progress through grammar and high school and had not interfered with her carrying on a more or less normal existence. Such an orbital mass originating from an optic nerve tumor has certain unusual features which are worthy of report.

COMMENT

It is generally accepted that a so-called glioma of the optic nerve is a benign, slowly growing, rare tumor, doubtless a manifestation of Recklinghausen's disease, which appears in the first or second decade of life and is characterized by a slowly progressive, painless exophthalmos with optic atrophy and diminution of vision. The diagnosis, although not absolutely certain, may usually be made by x-ray evidence of enlargement of the optic foramen in conjunction with the above-mentioned symptoms and signs. The pathogenesis of the tumor is not yet completely definitive, the most recent work pointing toward an astrocytoma or an oligodendrocytoma. Although a few favorable reports regarding irradiation of these tumors have been published, surgery is the basic form of treatment, and the literature contains considerable disagreement as to the best method of surgical approach; it is also the experience found in the literature that enucleation of the globe with as much as possible of the optic nerve will prohibit future recurrence; this is in complete contrast to what occurred in this case. Since it is not improbable that a glioma of the optic nerve is part of a systemic disease present in the first decade of life, a patient with this lesion should be subjected to a routine and careful investigation, and the treatment of the patient's condition is within the province of the internist, and not the ophthalmologist alone.

In conclusion, a case of glioma of the optic nerve is here recorded, proved by pathologic examination following enucleation of the globe, which exhibits a triad of striking and unusual features:

1. It shows a massive recurrence taking place over a period of 22 years following excision of the eyeball, which in itself is quite contradictory to the experience found in the literature.

2. Its slowness of growth, occurring over a period of 22 years, without involvement of the chiasm or intracranial tissue during this entire time, constitutes an almost unparalleled period for the existence of an orbital recurrence, while simultaneously the patient is allowed a comparatively normal life.

3. The slowness of growth over this long period emphasizes very strikingly the lack of malignancy and the failure of these tumors to metastasize.

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BIBLIOGRAPHY

Davis, F. H.: Primary Tumors of the Optic Nerve: A Phenomenon of Recklinghausen's Disease, Arch. Ophth. **23**:735 (April); 957 (May) 1940.

Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. III, St. Louis, C. V. Mosby Company, 1941, pp. 3080-3089.

Marshall, D.: Glioma of the Optic Nerve as a Manifestation of von Recklinghausen's Disease, Tr. Am. Ophth. Soc. **51**:117-155, 1953.

Reese, A. B.: Tumors of the Eye, New York, Paul B. Hoeber, Inc., 1951, p. 150.

Verhoeff, F. H., in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, Vol. III, 1932, pp. 1029-1039.

Annual Reviews

PHARMACOLOGY AND TOXICOLOGY

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A REVIEW of the literature pertaining to the pharmacology of certain agents the ophthalmologist may use is presented. There have been relatively few new developments in this field during the year under review, most of the published material only extending or affirming previous knowledge. The majority of reports concern experimental and clinical studies of the corticosteroids and antibiotics.

The coverage is necessarily broad in scope because the ophthalmologist increasingly administers medications systemically—medications which often have profound general, as well as ocular, effects. The bibliography includes only representative articles published during the past year. Prior studies, many of which have been documented in previous reviews, are mentioned to provide continuity.

CORTICOTROPIN AND THE CORTICOSTEROIDS

The rate of corticotropin release by the pituitary gland is reduced when lesions are made in the hypothalamus, particularly lesions in the supraopticohypophyseal system.* Intravenously injected corticotropin disappears very rapidly from the blood stream. It is not readily demonstrable in the blood of normal subjects but can be detected in patients with untreated Addison's disease.[3] The hormone is excreted, however, in the urine of normal persons.[4] In an isolated adrenal gland preparation, definite corticosteroid production can be evoked by small concentrations of corticotropin, i. e., 0.001 I. U. per liter of perfusate; maximum production results when the concentration reaches 0.1 I. U. of corticotropin per liter.[5] Stimulation of the adrenal gland persists for a few hours after corticotropin is withdrawn.† This accounts only in part for the good therapeutic response produced by intravenous administration of the drug for 8 of a 24-hour period. Circulating corticosteroids depress pituitary output of corticotropin, and their exogenous administration, consequently, suppresses adrenocortical function. This suppression can be prevented by the simultaneous administration of corticotropin.[9]

Among the major changes induced by corticotropin in the adrenal gland are hyperplasia, a decrease in ascorbic acid concentration, and the synthesis of various corticosteroids. Of these, the so-called mineral corticoids and the glucocorticoids are of greatest interest to the clinician. The mineral corticoids include desoxycorticosterone and aldosterone,‡ the latter being a recently identified steroid which causes greater sodium retention than desoxycorticosterone. The mineral corticoids have no anti-inflammatory effect. Indeed, they may inhibit the anti-inflammatory effect of the glucocorticoids.[13]

The glucocorticoids of clinical significance are hydrocortisone and cortisone. Hydrocortisone is the corticosteroid released in greatest quantity into the blood stream of man.[14] Cortisone is probably not produced in significant amounts. The general metabolic effects of these two hormones, however, are similar in kind, although differing in degree, for hydrocortisone is approximately twice as potent as cortisone. Their major metabolic actions have been discussed fully in previous reviews and are only briefly summarized

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* References 1 and 2.

† References 6 to 8.

‡ References 10 through 12.

here. First, they stimulate gluconeogenesis from protein and, possibly, from fat [15]; consequently, they may effect a negative nitrogen balance. Second, the glucocorticoids alter mineral balance, causing renal retention of sodium and excretion of potassium. An elevation of the blood pressure may accompany this altered cation balance, although a causal relationship is not certain. Also, the distribution of electrolytes at the cellular level is apparently affected by these hormones.[16]

At the tissue level, the glucocorticoids have diverse metabolic effects. Among those reported during the last year are a depression of the R. Q. of adipose tissue [17] and a cortisone-induced decrease in the hexosamine content of certain tissues.[18] As measured by dyes, corticotropin and cortisone appear to alter the oxidation-reduction systems of the skin, having an effect somewhat opposite that of sulfhydryl-containing compounds, such as glutathione.[19] This observation is interesting in the light of a separate study showing that the cortisone block of the sensitivity reaction to tuberculin can be overcome by a sulfhydryl compound, cysteinamine.[20]

Systemic administration of corticotropin, cortisone, or hydrocortisone elicits an eosinopenia of such reproducibility that it provides a useful laboratory measure of response to the drugs. The cause of the eosinopenia is not fully known, but there is evidence that it does not result from destruction of eosinophiles by the hormones.[21] In addition, lymphocytopenia, possibly due to lytic action on the lymphocytes,[22] and leucocytosis may result from administration of the drugs.

The glucocorticoids elicit a number of effects which are collectively termed "anti-inflammatory" or "antiphlogistic." First, they alter the responsiveness of the vascular bed. For example, cortisone reduces the vascularization which develops in a tissue subjected to a noxious stimulus.[23] This may, in some measure, be due to a change in vascular tone. Cortisone does not increase the responsiveness of the vascular bed to pressor drugs.[24] On the other hand, following the administration of corticotropin, the terminal vascular bed of the eye shows increased reactivity to both adrenergic and cholinergic drugs and to sympathetic stimulation.§ Second, the hormones reduce the accumulation of inflammatory cells, fibrin deposit, and other classic signs of inflammation. Evidence has been presented in past reviews that such activity of the hormone may result from inhibition of a substance, leucotaxin, released at the site of injury. It has not been established firmly, however, that such a substance exists.[27] Third, fibroblastic response is decreased by these agents. Thus, their suppression of fibroblastic growth in tissue culture can be demonstrated.[28] This would account, partly, for the impaired wound healing which may occur when the drugs are administered. (Tissue culture growth of epithelium is uninhibited by the corticosteroids, however. Indeed, cortisone has been reported to increase the mitotic rate in the corneal epithelium of the experimental animal.[29])

From these, and other, effects stems the beneficial response induced by the hormones in a variety of clinical conditions, including the hypersensitivity reaction. The tuberculin type of hypersensitivity reaction is the one most likely to be blocked by the drugs.

The particular chemical configuration of the steroids which confers anti-inflammatory, in contrast to the more obvious metabolic, effects is not known with certainty. Insertion of a halide into the 9-alpha position of hydrocortisone produces a drug with potent antiphlogistic activity.[29] However, this modification also increases the sodium retention caused by the hormone.[31] Of the halide derivatives, 9-alpha-fluorohydrocortisone is apparently the most potent.‖

That compounds can be developed which are quite devoid of metabolic function, while retaining antiphlogistic action, is demonstrated by recent studies of two new steroids, prednisone and prednisolone. These are analogues of cortisone and hydrocortisone, respectively, formed by introduction of a double bond into the steroid nucleus.[34]

§ References 25 and 26.

‖ References 32 and 33.

Early reports indicate that they do not have the usual metabolic effects of the 17-hydroxycorticosteroids and yet show anti-inflammatory activity, as indicated by the favorable clinical response in the treatment of rheumatoid arthritis.[35] Milligram for milligram, they are said to have greater anti-inflammatory activity than cortisone or hydrocortisone.

Except in ocular structures, cortisone is quite ineffective when administered locally (e. g., to the skin or joint). Local application of hydrocortisone, however, usually produces good clinical response. More objective measures have demonstrated a difference between the hormones, as well. Thus, comparison of the influence of the two steroids on the spreading of a dye in the skin demonstrated that in certain collagen diseases the rate of spread of injected dye is increased by cortisone and decreased by hydrocortisone.[36] It has been postulated that the local effectiveness of hydrocortisone, as compared with cortisone, is due to the fact that the former is less soluble, hence remains longer at the site of application. However, injection into joints has demonstrated that the two compounds persist for an equal length of time at the site of injection and enter the cell with equal facility.[37] Another hypothesis suggests that hydrocortisone is the active glucocorticoid, the effect of cortisone being due to its conversion to hydrocortisone. If such is the case, then ocular tissues, as distinct from other tissues in the body, must be capable of transforming cortisone into hydrocortisone, since both are locally effective in ocular disease.

Available reports indicate that corticosteroids are present in normal aqueous [38] and that their concentration increases following administration of corticotropin.[39] One study has shown that, following subconjunctival injection, cortisone penetrates to the aqueous better than hydrocortisone.[40]

Clinical Use.—The most certain clinical response from corticotropin is obtained when 20-25 units of the drug is administered by intravenous drip over a period of six to eight hours in dextrose solution. A long-acting gel, given subcutaneously or intramuscularly once a day in doses of 20-40 units (sometimes more), is probably equally effective. Intramuscular injection of the short-acting aqueous form gives less predictable response. The degree of depression of the eosinophile count has been employed widely as a laboratory measure of the corticotropin effect. However, the degree of eosinopenia and the clinical effect may not be exactly parallel. Probably the best laboratory measure of corticotropin response is the increase in concentration of circulating 17-hydroxycorticosteroids.

For systemic effect, hydrocortisone and cortisone preferably are given orally, although preparations for parenteral use are available. Oral administration of the steroids produces a higher plasma level of 17-hydroxycorticosteroids in patients with pernicious anemia than in normal persons.[41] Thus, some of the orally administered hormone may be destroyed by the normal gastrointestinal tract. The amount of circulating 17-hydroxycorticosteroids can be maintained at a higher level after injection into the experimental animal when ascorbic acid is administered simultaneously.[42] There is no evidence, however, that such administration has clinical value.

The initial dose of cortisone usually given the adult patient orally is 300 mg. per day, administered in divided quantities every six hours. The maintenance dose, generally 25 to 100 mg. per day, varies with the circumstances. The equivalent clinical dose of hydrocortisone is one-half to two-thirds that of cortisone. For local use in the eye, the steroids are available in suspension and ointment form in concentrations ranging from 0.5% to 2.5%. The aqueous suspension is suitable for subconjunctival injection. The drugs are also marketed in combination with antibiotics, such as neomycin, oxytetracycline, and tetracycline. A thorough discussion of the administration of the corticosteroids in ophthalmic practice has appeared recently.[43]

There is some clinical evidence that hydrocortisone may be beneficial in ocular disease when cortisone is ineffective.[44] Generally, however, the therapeutic response to cortisone is about equal to that of hydrocortisone when either is used in clinically effective systemic dosage. In the final analysis, though, the ratio of clinical effectiveness to toxic manifestations appears to favor hydrocortisone.

The general clinical use of these agents in ophthalmology has been reviewed during the past year.¶ Current thought emphasizes that the indications for use of the drugs should derive from a consideration of the altered physiology of a particular disease. It has been stressed that the drugs are not curative, but derive their greatest clinical usefulness from the protection they afford against acute inflammatory processes resulting from some physical, chemical, or bacterial agent. The corticosteroids are very effective in the treatment of the allergic or hypersensitive affections of the eye. The consensus of laboratory and clinical experience indicates that treatment of anterior-segment disease usually requires only local hormone application (including subconjunctival). Parenteral or oral administration is required in treating disease of the posterior segment.

Specific reports during the year under review include the following: Topical administration has proved of value in the treatment of interstitial keratitis # and atropine hypersensitivity.[51] Cortisone and corticotropin are said to be beneficial in the treatment of herpes zoster ophthalmicus, relieving pain and suppressing the inflammatory response.[54] The drugs are reported to be helpful in the treatment of ocular complications of sarcoidosis.* Their worth is questionable, except as a supportive measure, in the treatment of Sjögren's syndrome,[57] pemphigus,† and the Stevens-Johnson syndrome.‡ The drugs are probably ineffective in the treatment of degenerative diseases of the eye, although an occasional encouraging report appears.[62] It is generally agreed that the agents are probably of no value in progressive exophthalmos of presumed endocrine origin. Corticotropin may, as a matter of fact, promote the exophthalmos produced experimentally by anterior pituitary extract, although neither it nor cortisone, injected alone, appears to cause proptosis.[63] Yet occasional reports attest to the fact that the hormones may be of benefit in certain cases of exophthalmos.§

The same general pattern of use has prevailed in other fields of medicine. The steroid hormones have been found beneficial in certain hypersensitive states, many of the so-called collagen diseases, some arthritic conditions, particular chronic skin diseases, etc.‖ As has been mentioned in previous reviews, the specific indications for the use of these agents are being defined more clearly and their employment, consequently, is becoming more restricted. Critical appraisal has indicated that in certain instances older forms of therapy are possibly as good. For example, studies comparing acetylsalicylic acid with corticotropin or cortisone in the management of rheumatoid arthritis [74] and rheumatic fever [75] have failed to uncover definite superiority of the hormones over the salicylates.

Hazards from Use of the Hormones.—The local ocular use of cortisone or hydrocortisone is not without hazard.¶ Serious complications may result from their use in the presence of infection not controlled by antibiotics, particularly virus infections, such as herpetic keratitis. No reaction has been described which can be construed as a hypersensitivity to locally administered cortisone or hydrocortisone. An increase in ocular tension during the local treatment of uveitis with cortisone has been reported.[76] A more serious elevation in tension was reported to

¶ References 43 and 45 to 49.

References 50 through 52.

* References 55 and 56.

† References 58 and 59.

‡ References 60 and 61.

§ References 64 and 65.

‖ References 66 through 73.

¶ References 76 and 77.

follow the administration of corticotropin to patients with uveitis.[79] It has been demonstrated by both experimental and clinical studies that in the usual clinical dosage the drugs do not impair healing of ocular wounds.# Although intravitreal injection has been recommended for the treatment of posterior segment conditions, conclusions regarding the efficacy of this procedure must be guarded.

Reports of untoward reaction to systemic administration of these hormones continue to appear, but little new information has come to light. The dangers arising from the lowered resistance to infection which may accompany the systemic use of the drugs have been emphasized.[82] Experimental studies have demonstrated the hazard of administering these hormones in the presence of fungous infection [83] or tuberculosis.[84] Activation of a peptic ulcer and its subsequent perforation may occur. Hypertension may appear or, if present, may worsen. Diabetes is no contraindication, except possibly in the presence of diabetic retinopathy or nephropathy. Although experimental results have demonstrated an adverse effect on the fetus of the pregnant animal treated with these hormones,* therapy during human pregnancy without untoward fetal reaction has been reported.[87] As a general policy, a low-salt, high-protein diet with added potassium is recommended when the hormones are administered systemically in full therapeutic dosage.

CHEMOTHERAPEUTIC AGENTS

Antibiotics and Sulfonamides

The pattern of use of antimicrobial agents in a community hospital has been analyzed in a recent report.[88] The report showed that some 42% of the patients discharged during one month had received, orally or parenterally, one or more antimicrobial agents during their hospital stay. The percentage was higher if newborn infants and obstetrical patients were excluded from the census. The drugs were administered more frequently to surgical than to medical patients and oftener for prophylaxis than for control of active infection.

Mode of Action.—Past reviews have emphasized three types of activity through which these drugs may exert their antimicrobial action: (1) a lytic surface effect; (2) an antimetabolic effect, i. e., interference with the metabolism of the bacterial cell by competition with some chemically similar metabolite, and (3) the inhibition of certain essential cellular enzymes. In many instances, they appear to interfere with synthesis, e. g., of proteins, rather than with a degradative process, e. g., respiration.† This may account for the specificity of the various antibiotics and for the clinically and experimentally observed fact that these drugs are most effective in combating a rapidly growing, rather than a static, bacterial population.

In addition, both clinical and experimental [92] results demonstrate that the response of the host organism is of considerable importance, that in the absence of host cooperation the antibacterial action of the antibiotics is reduced, and that the antibiotic may heighten body defenses by altering the virulence of the invader.

Bacterial Resistance.—Two patterns of bacterial resistance to the antibiotics have clinical significance. The first is the resistance developed by an infective strain during treatment. Resistance of susceptible strains to an antibiotic can be developed readily in the laboratory but, other than with streptomycin, is seldom acquired during treatment of an active infection. The apparent development of bacterial resistance during clinical therapy is probably often due to cross infection with a resistant strain of the same bacteria.[93]

The other facet of this problem concerns the repeated isolation, over a period of years, of increasing numbers of bacteria resistant to antibiotics. The organism most frequently incriminated is the Staphylococcus. (A marked increase in the incidence of antibiotic-resistant strains of other bacteria, such

References 80 and 81.

* References 85 and 86.

† References 89 to 91.

as the streptococci, has not been demonstrated.[94]) In a given community, the frequency with which staphylococci resistant to a given antibiotic are encountered depends, at least in part, upon the frequency with which that agent is prescribed.[95] The increasing resistance of the staphylococci may eventually prove serious. The fatalities resulting from staphylococcal septicemia or pneumonia have increased in recent years.[96]

Among the possible mechanisms by which resistance develops are (1) the natural survival of individual organisms, which produce a substance, such as penicillinase or chloramphenicol reductase, that inactivates the antibiotic; (2) alteration of the metabolism of the organism so that the particular metabolic function affected by the antimicrobial agent is no longer essential for the survival of the cell, and (3) the development of mutant strains with an inherent resistance.

Absorption and Tissue Distribution.—There have been relatively few new studies of the penetration of chemotherapeutic drugs into the eye. Carbomycin was found to penetrate from the conjunctival sac or subconjunctival space into the aqueous humor of the experimental animal; higher concentration in the aqueous was achieved by iontophoresis. Intramuscular or intravenous administration produced detectable, but not particularly high, aqueous levels of carbomycin.[97] Radioactively marked penicillin was found to pass the blood-aqueous barrier of the normal eye poorly, but its concentration in the aqueous increased after paracentesis or experimentally induced infection.[98] Thus, failure of a drug to enter the aqueous of the normal eye in effective concentration does not prove it valueless in cases of infection. Other things being equal, those drugs with the greatest lipoid solubility and lowest molecular weight most readily enter the anterior chamber from the blood stream.[99] Of the commonly used antibiotics, chloramphenicol probably penetrates best. The sulfonamides, particularly the pyrimidine derivatives, also enter the aqueous readily from the blood stream.

Like its congeners chlortetracycline[100] and oxytetracycline, tetracycline appears in effective concentration in the serum after ingestion of the usual dose, i. e., 500 mg. every six hours.[101] Intramuscular administration of significantly smaller quantities of oxytetracycline (100-200 mg. every six to eight hours), and, presumably, the others as well, produces adequate serum concentration.‡ Subcutaneous administration of the drug (5 mg. per pound of body weight every 12 hours) is also effective and valuable in infants.[104]

Benzathine penicillin G (*N,N'*-dibenzylethylenediamine dipenicillin G), a highly insoluble salt, is more stable and is absorbed more slowly than penicillin procaine or penicillin G after oral or intramuscular administration.§ Therapeutically effective blood levels are said to be maintained for several days following one intramuscular injection of this salt; for this reason it has been recommended for single-dose therapy, particularly in the prophylaxis of such diseases as rheumatic fever.‖

Effective therapy may not require maintenance of constant plasma concentrations of an antibiotic, since tissue concentrations probably fluctuate less than plasma levels.[112] Moreover, cure of an infectious disease process is more than a simple titration of the antibiotic against the organism; the defense mechanisms of the host play a great role in combating infection.[113] Spacing of the dose at equal time intervals may, thus, not be so important as has been thought previously.

Hazards of Antibiotic Therapy.—One of the hazards of antibiotic therapy is superinfection (overgrowth of a resistant organism not the cause of the primary infection).[114] In one comprehensive study of this problem, it was shown that 2.19% of 3095 patients given a chemotherapeutic agent developed a superinfection, its signs most frequently becoming evident on the fourth or fifth day after initiation of antimicrobial therapy.[115] Among the factors predisposing to

‡ References 102 and 103.
§ References 105 to 107.
‖ References 108 to 111.

a superinfection were (1) an age of 3 years or less, (2) the use of a drug or combination of drugs with a broad antibacterial effect, and (3) primary disease of the lower respiratory tract or the middle ear. Superinfections with Candida albicans have been encountered occasionally. This yeast, however, is a normal contaminant of many body cavities, and it has been suggested that C. albicans may not be the pathogen in many superinfections attributed to it.[118] When it does occur, the development of true moniliasis during antibiotic therapy is probably due to lowered host resistance to the yeast rather than to stimulation of its growth by the antibiotics.

The other important hazard attending the use of antibiotics is toxicity of the drugs to the human being. Hypersensitivity to the drugs is the most commonly encountered reaction. Penicillin and, to a less extent, streptomycin are the worst offenders. Reactions to penicillin vary from mild cutaneous manifestations to anaphylactic shock and death.¶ The other commonly used antibiotics, such as the tetracyclines, chloramphenicol, polymyxins, bacitracin, and neomycin, have been implicated rarely as sensitizing drugs.

Proof that a specific chemotherapeutic agent may cause a blood dyscrasia is often difficult to establish.[121] Chloramphenicol, however, appears to be such a drug[122] and, because of its myelotoxicity, is recommended for systemic use only in the treatment of typhoid or in other instances where it has proved to be the therapy of greatest merit. Renal damage is the major toxic manifestation which results from the systemic administration of the polypeptide antibiotics, bacitracin, and the polymyxins.[123]

The widespread systemic use of the tetracyclines stems partly from the fact that they can be given with little fear of severe side-reaction. The commonest reactions following the administration of these drugs are referable to the gastrointestinal tract and include loose, frequent stools and diarrhea.[124] Tetracycline appears to cause less gastrointestinal disturbance than either chlortetracycline or oxytetracycline.[125]

(It is important to note that the antibiotics tested do not interfere with the healing of epithelial defects in the cornea of the experimental animal.[126])

Clinical Use.—Although many proprietary preparations are available to the physician, the actual number of antibiotics in common use is quite small. A recent helpful manual lists the various trade names under which the individual drugs, or combinations thereof, are marketed.[127]

It is axiomatic that indiscriminate use of antibiotics is to be avoided and that laboratory tests which identify the organism and determine its sensitivity to the various chemotherapeutic drugs should be a guide to therapy wherever possible. As a general rule, those antibiotics, such as chloramphenicol, bacitracin, neomycin, and the polymyxins, which are not widely used systemically are preferred for local use. Local application of the tetracyclines does not appear to be contraindicated, since they are infrequent sensitizers.

Penicillin is still the preferred antibiotic for the systemic treatment of infections caused by the Gram-positive cocci and such Gram-negative cocci as the Gonococcus. It is the drug of choice in the treatment of syphilis[128]; indeed, against the Treponema pallidum it is uniformly effective. A study of the possible benefit to be derived from routine administration of penicillin to patients with penetrating ocular injuries has indicated that prophylactic treatment significantly reduces the incidence of subsequent infection and the necessity for eventual enucleation.[129]

Erythromycin has an antibacterial spectrum similar to that of penicillin,[130] as does carbomycin. Erythromycin is also quite effective against diphtheria.[131] The primary indication for the use of erythromycin is bacterial infection which is resistant to penicillin, particularly a staphylococcal infection.[132] Local application of the drug has proved beneficial

¶ References 117 to 120.

and well tolerated in the treatment of certain ophthalmic infections.[133] Trachoma is reported to respond to erythromycin,# although not remarkably better than to other forms of therapy.

During the past year, tetracycline has been the most widely studied of the broad-spectrum antibiotics.* This drug has an antibacterial activity similar to its congeners oxytetracycline and chlortetracycline, but has come into prevalent use because of its lower toxicity. While the antibacterial spectra of the three compounds generally are considered the same, this may not invariably be true. One study demonstrated that more strains of staphylococci were resistant to tetracycline and to oxytetracycline than to chlortetracycline.[141] Cross resistance between the tetracyclines may be encountered clinically.[142] Of the other broad-spectrum antibiotics, chloramphenicol is certainly the most effective. Its local use in ocular infections is recommended.[143] Moreover, it may be the drug of choice in certain ocular infections which require systemic therapy, such as postoperative endophthalmitis.[144] A similar clinical situation presents in meningitis, in which chloramphenicol has proved to be of value.[145]

The infrequent systemic use of neomycin and its rather wide antimicrobial activity adapt it to the treatment of external disease by topical application. Recommendations for its local use in ophthalmic infections[146] and in pyogenic skin diseases[147] have appeared.

The polymyxins deserve comment, since they are the most effective drugs against Pseudomonas aeruginosa. In the treatment of experimental corneal ulcers due to this organism, the efficacy of the polymyxins has been reported again.[148] Polymyxin B may be lifesaving in cases of meningitis due to P. aeruginosa.[149] The polymyxins should be considered, too, in treating an infectious process due to any of the Gram-negative rods.

Reports have appeared of varying success in the treatment of trachoma by various chemotherapeutic agents, including the sulfonamides and the broad-spectrum antibiotics, e. g., chlortetracycline, oxytetracycline, and chloramphenicol.† Of these, the sulfonamides are perhaps the most effective. Combined systemic and local administration of these drugs is generally recommended. In one rather large series, copper sulfate-methylene blue treatment appeared to be more effective than chlortetracycline, oxytetracycline, or sodium sulfacetamide.[151] In this paper the authors appropriately mention that in recommending any therapeutic regimen the problems of mass medication must be considered.

Combinations of Antibiotics.—A combination of antibiotics is administered generally for one of two reasons: First, the spectrum of antibacterial coverage may be widened by the administration of two drugs, one effective largely against Gram-negative and the other against Gram-positive organisms. Such coverage tends to prevent superinfection. For this purpose, polymyxin is commonly combined with an antibiotic, such as bacitracin or erythromycin, that is effective against Gram-positive organisms.‡

The second purpose of administering two (or more) antibiotics is to achieve a synergistic effect. Synergistic activity can be identified readily in the laboratory but may not be always so evident clinically. Laboratory studies have demonstrated that polymyxin B and neomycin are strongly synergistic,[157] and other examples of experimental synergism can be gleaned from the literature.§ Clinical evidence of a synergistic effect of combinations of antibiotics is also available.[160] However, mixtures of antibiotics may be simply additive,[161] or actually antagonistic. In the final analysis, as has been emphasized in previous reviews, each case of infection should be considered individually, and the use of an antibiotic combination for a synergistic effect must rest upon laboratory studies, followed by subsequent clinical observation.

References 134 and 135.

* References 136 to 140.

† References 150 to 152.

‡ References 154 to 156.

§ References 158 and 159.

Antituberculous Agents

Included in the group of antituberculous agents are streptomycin, isoniazid, and paraaminosalicylic acid. New derivatives of the last two agents have been synthesized, but none has proved superior to those in common use.‖ Streptomycin has been used for the longest period. Since the tubercle bacillus readily develops resistance to this drug, a public health hazard may conceivably result from its use. Specific study has not demonstrated such a hazard, however.[164]

Successful treatment of various tuberculous infections with isoniazid (isonicotinic acid hydrazide) has been reported.¶ Generally, however, clinical results indicate that treatment of tuberculosis with combinations of isoniazid and streptomycin (and possibly PAS, in addition) is the method of choice,# resistance of the tubercle bacillus to any one drug being less likely to develop during the combined therapy.[171] Oxytetracycline, also, is said to delay the development of resistance to isoniazid used in the treatment of pulmonary tuberculosis.[172]

As mentioned in previous reviews, isoniazid readily crosses the blood-aqueous barriers, whereas streptomycin does not. The successful treatment of ocular tuberculosis in the experimental animal with isoniazid has been reported,[173] the authors emphasizing the importance of continuing treatment beyond apparent clinical cure, to prevent late recurrences of infection. Treatment of suspected tuberculous involvement of the uveal tract and other structures of the human eye with this drug is reported to be efficacious.[174] Also, a case of primary tuberculosis of the conjunctiva has been reported to respond to systemic streptomycin and PAS.[175] Again, however, when suspected ocular tuberculosis is to be treated actively, administration of both isoniazid and streptomycin (and, possibly, PAS as well) is preferred. The recommended dosage is 1 gm. of streptomycin every other day or three times weekly, 12 gm. of paraaminosalicylic acid daily, and 300 mg. of isoniazid daily, in divided doses. Under such treatment, clinical improvement of ocular disease should be noted within two weeks.[176] Failure to observe any improvement after three weeks of therapy indicates that the process is probably not tuberculous. It is emphasized, again, that these drugs are primarily bacteriostatic and that the ultimate cure rests upon mobilization of the host's defenses.

Side-reactions from these drugs are not too frequent if the doses indicated above are employed. Drug reactions to paraaminosalicylic acid include fever, rash, nausea, emesis, and muscular and joint symptoms.[177] They generally subside when the drug is withdrawn. Paraaminosalicylic acid has certain antithyroid activity, but this is not of clinical significance, except, possibly, during prolonged therapy.[178] A toxic effect of streptomycin on the eighth cranial nerve is not likely to appear under the schedule of administration recommended here. The most prominent side-effect of isoniazid is a neurologic disturbance manifested as a peripheral neuropathy, convulsive tendency, or psychosis.* These manifestations of altered nerve tissue metabolism may be due to a pyridoxine deficiency.[182] Administration of pyridoxine appears to prevent the development of peripheral neuritis.[183] The onset of Reynaud's phenomenon during administration of isoniazid, in an otherwise normal person, has been reported.[184] This may correlate with the observed fact that this drug potentiates the activity of sympathicomimetic amines.[185] Iproniazid, the isopropyl derivative of isoniazid, has proved to be much more toxic than isoniazid and is not recommended for human use.

Antiparasitic Agents

Interest in the antiparasitic compounds stems from the observation that at least one, pyrimethamine (Daraprim), may be effective against the Toxoplasma parasite.[186] A diaminopyrimidine derivative, it is an efficient antimalarial drug. Pyrimethamine has certain anti-folic-acid activity; from this prob-

‖ References 162 and 163.

¶ References 165 to 167.

References 168 to 170.

* References 179 to 181.

ably stems its usefulness in the treatment of polycythaemia rubra vera.[187] In the active treatment of malaria, a dosage of 50 mg. on each of two successive days has proved efficacious; a prophylactic dose of 25 mg. weekly has been recommended.[188] The dosage and duration of treatment in cases of uveitis attributed to the Toxoplasma organism have not been established finally. Simultaneous treatment with pyrimethamine and sulfonamides is being tested. Pyrimethamine may seriously depress bone marrow activity; consequently, when prolonged treatment is utilized, close supervision is essential. A fatality resulting from accidental overdosage has been reported,[189] terminal signs being convulsions, followed by circulatory collapse.

During the year, a sulfone compound was reported to be of value in the treatment of experimentally induced Toxoplasma infection of rabbits.[190] The authors suggested that, in addition to chemotherapeutic inactivation of the parasite, allergy to the organism should also be treated, preferably with one of the corticosteroids. As in the treatment of tuberculous uveitis, the major problem is still one of diagnosis.

Other uses of some of the antimalarials (the quinoline derivatives), particularly quinacrine (Atabrine), include the treatment of certain skin diseases in which sensitivity to solar radiation plays a role.† The mechanism of their action in these instances is not understood.

Other Agents

While selenium sulfide is not strictly a chemotherapeutic agent, its use is included here. This compound is effective in the treatment of seborrheic dermatitis[194] of the scalp. It is not a cure, however, and treatment must continue. Successful treatment of blepharitis marginalis with the drug in an ointment base has been reported.[195]

AUTONOMIC DRUGS

Cholinergic and Parasympathomimetic Drugs

According to the nomenclature previously used, cholinergic drugs are considered to be those which act directly on the effector organ, e. g., the iris sphincter or ciliary muscle. They include acetylcholine, carbachol, methacholine, and pilocarpine and are effective on the denervated preparation. Of these, the first three, but not the last, are hydrolyzed with varying rapidity by cholinesterases.

Nothing new concerning the ocular pharmacology of these agents has been published during the past year. One publication proposes that pilocarpine be used as an antagonist to the undesired side-effects of ganglion-blocking agents used in the treatment of hypertension.[196] These side-effects result from blockade of the parasympathetic ganglia.

The parasympathomimetic drugs block the action of cholinesterase and, by permitting the accumulation of acetylcholine, cause a motor response in the parasympathetically innervated effector organ. Denervated (postganglionic) preparations do not respond to these drugs. There are, in general, two different chemical (and physiologic) types. The first, exemplified by physostigmine, reversibly inhibits cholinesterase and has a relatively short action. The second group is composed of the phosphate esters, of which isofluorophate (diisopropyl fluorophosphate) is the best-known example. These irreversibly inhibit cholinesterase activity and produce a longer and more intense response. The sites of action of these two groups on the enzyme are, apparently, different. They are, to a certain extent, competitive. Among the newly developed anticholinesterases is one (bis-[dimethylamido]-fluorophosphate) which may prove clinically useful, since it appears as potent as isofluorophate but causes fewer undesirable side-effects.[197]

During the past year additional reports of untoward ocular response to the anticholinesterase agents have appeared. These have included three reports on the development of pigment nodules at the pupillary margin following the local application of these strong miotics.‡ Detachment of the retina following the use of isofluorophate has been reported,[201]

† References 191 to 193.

‡ References 198 to 200.

but a causal relationship between the administration of the drug and the detachment cannot be considered to be established. Lastly, intracarotid injection of some of the more potent cholinesterase inhibitors has been shown to cause cataract in experimental animals.[202] However, nothing suggests that local use of these drugs may be similarly toxic. Isofluorophate and other such anticholinesterase drugs are toxic to the central nervous system. The mode of action is not known, but the toxicity cannot be attributed solely to cholinesterase inhibition.§

Carbonic Anhydrase Inhibition.—The carbonic anhydrase inhibitors are considered here because they, as well as the miotics, are used in treating glaucoma. The most commonly used carbonic anhydrase inhibitor is acetazoleamide (Diamox).

Carbonic anhydrase is widely distributed in the human body, and inhibition of the enzyme might be expected to have relatively profound effects. Acetazoleamide affects many secreting organs. For example, it may alter salivary gland activity, decreasing the sodium and bicarbonate concentrations of saliva.[205] However, the composition of sweat is not altered by a carbonic anhydrase inhibitor.[206] Acetezoleamide does not markedly affect the activity of all cells containing the enzyme. Thus, the blood transport of carbon dioxide, which requires a functioning carbonic anhydrase system in the red cell, is little altered by the usual therapeutic dose of these drugs. Alteration of kidney tubular function by acetazoleamide, however, is marked, and administration of the drug results in the excretion of an alkaline urine, containing increased quantities of sodium and potassium.[207] Because of this, the drug has proved useful as a diuretic in congestive heart failure and other conditions where extracellular salt accumulation has occurred. A decrease in the bicarbonate content of the plasma ensues. To this is attributed the benefit reported in the treatment of chronic emphysema.[208]

§ References 203 and 204.

Administered systemically, either by the oral or by the intravenous route, acetazoleamide has been found to have a marked ocular hypotensive effect, particularly when the pressure is abnormally elevated.‖ The mechanism by which acetazoleamide lowers the ocular tension is not fully known. The drug is not effective when applied locally. Parenteral administration of the inhibitor to the experimental animal markedly depresses carbonic anhydrase activity in anterior uveal tissue.[212] Probably as a result of this inhibition, the formation of aqueous humor by the ciliary body is reduced and thus the intraocular pressure is lowered.[213] The fact that the drug also appears to slow the formation of cerebrospinal fluid and lower the cerebrospinal fluid pressure [214] would fit this scheme, since the elaborations of the two fluids are probably physiologically similar. To date, the drug has been most valuable for the treatment of acute congestive and secondary glaucoma. It also lowers the tension in the chronic glaucomas. However, its ocular hypotensive effect diminishes with time.

The dose employed for the treatment of glaucoma varies, of course, with the circumstances. In acute cases, 250-500 mg. of acetazoleamide is usually effective. For chronic administration (usually in combination with miotics), doses of 125-250 mg. once daily to 500-1000 mg., in divided doses, have been employed. The toxicity of the drug, in the usual clinical dose, is not marked. Among the common side-effects are paresthesias. Acetazoleamide may cause the drug reactions seen with the sulfonamides, such as an agranulocytosis [215] and a febrile reaction.[216]

The Parasympathetic-Blocking Agents

Parasympathetic-blocking agents inhibit the response of parasympathetically innervated structures to the cholinergic and parasympathomimetic drugs and to parasympathetic stimulation. In most instances, blockade probably results from the drug competing with acetylcholine for the receptor. The usual ocular effects are iridoplegia and cyclo-

‖ References 209 to 211.

plegia. A rise in tension may also occur when the drugs are instilled in glaucomatous eyes.[217] This is usually ascribed to an embarrassment of drainage at the chamber angle; such a conclusion is, perhaps, an oversimplification.

Among such drugs marketed in recent years, and most useful to the ophthalmologist, is cyclopentylate (Cyclogyl), which produces an effective cycloplegia and iridoplegia of shorter duration than does atropine.[218] The side-effects from local application of cyclopentylate are minimal. Another drug, oxyphenonium (Antrenyl), in a 5% solution, causes a more prolonged cycloplegia and iridoplegia than does 1% atropine.[219] In 1% solution its activity is said to approximate that of 1% atropine.[220] It is recommended as an atropine substitute in patients hypersensitive to this drug. Occasionally, ocular use of atropine causes serious systemic toxicity.[221] The toxic manifestations of these agents include rapid pulse; dry, flushed skin, and central nervous stimulation.

Adrenergic and Sympathomimetic Drugs

The substance released at the sympathetic postganglionic nerve endings is probably levarterenol (nor-epinephrine, l-arterenol).[222] Epinephrine is the predominant hormone produced by the adrenal medulla. Of the two, levarterenol is the more potent pressor agent[223] and, consequently, is the drug of choice in the treatment of circulatory collapse of neurogenic origin.[224]

Both epinephrine and levarterenol are considered to be destroyed by an enzyme, amine oxidase, present at the sympathetic nerve endings. (There are certain objections to this hypothesis, however. One such is that the enzyme is not specific for epinephrine and levarterenol in the sense that true cholinesterase is specific for acetylcholine. Amine oxidase appears to be highly active against serotonin, a substance with pressor activity originally isolated from blood serum and later found in the central nervous system and other tissues. A recent review of the physiology and pharmacology of this interesting substance is available.[225]) The various adrenergic drugs are not inactivated at equal rates, perhaps accounting for the differences in their activity when applied locally to the eye. Drugs which inhibit amine oxidase have sympathomimetic activity. Cocaine is considered to be such a drug because it produces a mydriasis and potentiates the mydriatic action of epinephrine. Epinephrine is thought to possess both adrenergic and sympathomimetic (i. e., anti-amine-oxidase) activity.

By employment of perfusion experiments, it has been determined that the force and rate of contraction of the dilator fibers are proportional to the concentration of epinephrine.[226] Thus, the magnitude of response depends upon the number of receptor or effector cells stimulated by the drug, rather than on a graded response in the individual fibers. In addition to the usual effects attributed to sympathetic stimulation, locally administered epinephrine may lower the intraocular pressure of glaucomatous eyes. Levarterenol has a similar hypotonizing effect.[227] The exact mechanism by which these drugs lower the ocular tension is not known, although it has been suggested that epinephrine decreases the flow of aqueous humor.[228] The adrenergic agents may affect accommodation. Thus, the cycloplegic effect of homatropine was reported to be enhanced by the addition of phenylephrine (Neo-Synephrine) to the solution employed.[229]

Adrenergic-Blocking Agents

These substances act peripherally and block the effect of injected epinephrine or levarterenol and inhibit sympathetic stimulation. Among such drugs are certain ergot derivatives, such as the hydrogenated ergot alkaloids (e. g., Hydergine), substituted β-haloalkylamines,[230] and some imidazole derivatives, such as tolazoline (Priscoline).

The β-haloalkylamines, such as Dibenamine, lower the intraocular pressure when administered systemically. They appear to reduce the rate of aqueous humor formation and this may account for their hypotensive effect.[231] Hydergine also may lower the

ocular tension and has been suggested for preoperative treatment of glaucoma.[232] The means by which this drug lowers the tension is not known. Dihydroergotamine (not one of the alkaloids of Hydergine), given intravenously, is reported to reduce the permeability of blood-aqueous barriers in experimental animals,[233] but this effect cannot account for a hypotensive action.

Tolazoline, on the other hand, has been suggested as a provocative-test agent in the diagnosis of glaucoma. Injected subconjunctivally, the drug is said to cause a moderate increase in tension in the normal eye, but a much greater increase in pressure in over 50% of patients with glaucoma.[234] Side-effects included pain, conjunctival injection, and edema.

These compounds, by blocking sympathetic action, cause a passive vasodilatation. They are of value, therefore, in investigating the physiology of the normal and altered retinal circulation. Such studies are hampered by the fact that precise measurement of changes in the retinal circulation is difficult. As one such measure, the electroretinogram may prove useful.[235] From changes in the electroretinographic tracing, it has been concluded that tolazoline causes an increase in retinal blood flow.[236] Of other agents tested with this technique, papaverine and glyceryl trinitrate, which have a nonspecific vasodilatatory effect, caused a similar change, whereas both cervical sympathetic blockade and intravenous nicotinic acid were without effect. Change in the size of the angioscotoma has provided another gauge of the effect of vasodilators. In a recent study, the angioscotomas were observed to narrow in approximately half the subjects and to broaden in the remaining half, after administration of tolazoline.[237]

The effect of Hydergine on the retinopathy of hypertension has also been studied. (The action of this drug in hypertension cannot be attributed solely to peripheral blockade; rather, some central effect must also be postulated.) One group reported an improvement in the fundus picture and a return of the angioscotomas toward normal in a little over half the cases treated with Hydergine.[238] Other studies have indicated that the drug provides little benefit when fixed changes are present.¶ In general, the effect of the peripheral blocking agents and the nonspecific vasodilators, such as nicotinic acid, on the caliber of normal or diseased retinal vessels and on retinal blood flow is still relatively uncertain.

While not an adrenergic-blocking agent, adenosinetriphosphate is mentioned here, since it does cause a vasodilatation.[241] When injected intra-arterially, both ATP and ADP produce a prolonged vasodilatation, which resembles antidromic nerve stimulation.[242]

Ganglion-Blocking Agents

The ganglion-blocking agent most commonly employed is hexamethonium. However, many compounds variably block ganglionic transmission, including nicotine, atropine and many atropine-like compounds, and curare and curare-like drugs. These compounds vary in potency and, somewhat, in their mode of action.[243] The ultimate clinical picture resulting from ganglionic blockade depends upon the balance of residual sympathetic and parasympathetic activity.

Administration of hexamethonium has been reported in the past to lower the ocular tension, the drop in intraocular pressure perhaps resulting from the fall in arterial blood pressure. In addition, subconjunctival and retrobulbar injections of a potent ganglioplegic drug have been observed to cause a mydriasis and, often, a decrease in the retinal arterial pressure.[244] Of the ganglioplegic agents, particularly the methonium compounds have been used in the treatment of hypertension, and in some cases an improvement of the retinal picture, together with other favorable changes in the patient's course, has followed their administration.[245] Beneficial treatment of central serous retinitis with ganglioplegic drugs has been reported also.[246]

¶ References 239 and 240.

Antihypertensive Drugs Acting on Higher Central Nervous System Centers

For the medical treatment of hypertension there has become available a group of agents which, although their exact site of action is not known, probably act on higher nerve centers, such as the hypothalamus, or even the cortex. They include such drugs as hydralazine and the alkaloids of Rauwolfia serpentina, particularly reserpine and similar, more recently isolated alkaloids.# (The alkaloids of Veratrum viride appear to act by sensitizing in some manner the baroceptors of the aortic arch and carotid sinus, rather than by acting on the higher centers.[249])

The action of reserpine on the central nervous system is somewhat paradoxical. In experimental animals, it appears to lower the convulsive seizure threshold to electric stimuli and to antagonize the anticonvulsant action of diphenylhydantoin (Dilantin),[250] as well as other CNS depressants.[251] Nonetheless, reserpine has a definite tranquilizing and sedative effect on the patient. This may account for the benefit attributed to the drug in the treatment of disorders which have a psychogenic component.[252] Clinical use of reserpine in a variety of psychiatric disturbances is being studied intensively.[253] The dose of reserpine must be adjusted to the individual. It is deemed wisest to start with small doses, such as 0.1 mg. one to three times daily, increasing the dose gradually until the desired clinical effect (or toxicity) results.

These centrally acting drugs have proved valuable in the treatment of hypertension, particularly when a neurogenic element appears to play an etiologic role.* As currently practiced, the medical management of hypertension includes a combination of drugs acting on the higher centers with the ganglionic-blocking agents, as well as other therapeutic measures.†

Whatever the true etiology of the primary glaucomas, a neurogenic element undoubtedly plays a role in the course of the disease, and it is plausible that these or similar drugs acting on the higher centers may eventually prove valuable in its treatment.[261]

Among the serious side-effects of the Rauwolfia serpentina alkaloids is mental depression.[262] Other effects include nasal congestion, dyspnea, weakness, dreams, and nausea. The drug may have a miotic effect. Among the complications attending hydralazine therapy has been the appearance of some collagen-like diseases.‡

The Muscle Relaxants

Many of the muscle-relaxing drugs are pharmacologically similar to the ganglioplegic agents. Thus, drugs which block transmission at the motor end-plate also have slight ganglioplegic activity. Conversely, ganglioplegic drugs have some action as muscle relaxants. One or the other activity predominates, depending, in the methonium series in particular, upon the length of the carbon chain which separates the active (quaternary ammonium) groupings.[266]

The use of the muscle relaxants in ocular surgery continues to receive favorable comment.§ Interesting effects of curare on the ocular tension following electroshock have also been reported. A drop in the ocular tension was observed to occur during electroshock stimulus and to persist for some time after the shock. However, if the patients were curarized, electroshock caused a marked rise in ocular tension during the convulsive phase.[269] The cause of these effects of electroshock and curare on the ocular tension is not clear. Electroshock therapy of glaucomatous patients is said to increase severity of the glaucoma.[270]

Other muscle relaxants of potential value are those of the glycerol-ether group, including mephenesin and its carbamic acid ester. These block multineuron reflexes (polysynaptic) but not the monosynaptic arcs.‖ Their point of action appears to be at the brain stem

References 247 and 248.

* References 254 to 256.

† References 257 to 260.

‡ References 263 to 266.

§ References 267 and 268.

‖ References 271 and 272.

or spinal cord. They effectively reduce muscle spasm in a variety of conditions, including tetanus.¶

ANALGESIC COMPOUNDS

The Addicting Analgesics

The majority of reports during the year under review have concerned those compounds which block the toxic effects of morphine and other addicting analgesics. The best-known compound of this group is nalorphine.[275] Other morphine derivatives having similar activity have been synthesized,# but the goal of such research, namely, to produce a compound with the analgesic potency of morphine but bereft of its side-effects, has not yet been achieved. Nalorphine blocks multiple physiologic effects of many potent analgesics which are pharmacologically similar to morphine but differ from it chemically.[278] Nalorphine counteracts the respiratory and circulatory depression, the effect on the gastrointestinal tract, and the antidiuretic action of morphine.* A surprisingly small amount of nalorphine is required to antagonize the effect of the opiate analgesics. Thus, in experimental animals, it has been shown that the ratio of nalorphine to morphine necessary to block the significant side-effects of morphine, without altering its analgesic activity, varies from approximately 1:12, in the dog, to 1:30, in the mouse.[281] Moreover, administration of too much nalorphine may increase the total toxicity. Morphine, incidentally, does not appear to be antidotal to the toxic action of nalorphine.[282]

No such mixture of nalorphine and morphine has been recommended for human use. Nalorphine is used principally (in an intravenous dose of 5-10 mg.) in the treatment of an overdose of one of the addicting analgesics. Nalorphine has been considered ineffective against barbiturate intoxication,[283] although a recent report has indicated that it may counteract the respiratory depression induced by pentobarbital.[284]

One report has emphasized that the optimal dose of morphine is 10 mg. (1/6 grain) for a normal-sized person (70 kg.) rather than 15 mg. (¼ grain). The smaller dose is said to induce all the analgesic activity but fewer side-effects than the larger dose.[285] A survey of meperidine (Demerol) addicts admitted to a U. S. Public Health Service Hospital during a three-year period again emphasizes the addicting potential of this compound.[286] (Of the 457 meperidine addicts, nearly 50% were physicians, nurses, or persons connected in some way with the medical profession.)

The Antirheumatic Analgesics

The salicylates are, of course, the most prominent of this group. There is little doubt that the therapeutic benefit of these drugs in rheumatic diseases extends beyond the analgesia they produce.[287] This is due, at least in part, to the stimulation of the adrenal-pituitary axis.[288] However, the salicylates also exert metabolic effects not attributable to this stimulation. For example, the metabolic rate of both normal persons and patients with subacute rheumatic fever increases during administration of the salicylates.[289] Similarly, in vitro studies have indicated that in optimal concentrations sodium salicylate stimulates oxygen consumption of tissue slices, but depresses the oxygen uptake when the salicylate concentration is increased beyond the optimal level.[290] (In this respect, at the tissue level the salicylates act much like dinitrophenol.) The salicylates also are glycogenolytic.[291] In summary, a survey of the pertinent literature permits the conclusion that the antirheumatic activity of the salicylates may result partly from stimulation of the pituitary-adrenal axis, but may also be due to independent metabolic effects.

As previously noted, reevaluatory studies have indicated that in the treatment of the rheumatic diseases the salicylates compare favorably with corticotropin and the 17-hydroxycorticosteroids. There is a paucity of recent data concerning the use of salicylates in those ocular diseases which might feasibly respond to these drugs. Comparative study

¶ References 273 and 274.

References 276 and 277.

* References 279 and 280.

of the salicylates and corticosteroids in these conditions might prove interesting.

Phenylbutazone is the other antirheumatic analgesic that has been studied frequently during recent years. Its action does not appear to be mediated through the adrenal cortex. As with the salicylates, the clinical effect of phenylbutazone extends beyond its analgesic potency. Phenylbutazone reduces the permeability of the synovial membranes and periarticular tissues.[292] Some of the general metabolic effects of this drug have been reported in prior reviews. Study of its chemical derivatives has indicated that the antirheumatic or anti-inflammatory activity of phenylbutazone (like the steroids) is capable of being dissociated from metabolic effects, such as sodium retention.[293]

Clinically, the drug has been reported useful in the treatment of rheumatic disorders, such as rheumatoid arthritis and rheumatoid spondylitis.† In the former disease, it is perhaps as effective as the 17-hydroxycorticosteroids. Phenylbutazone probably has its greatest clinical usefulness in the treatment of gout.‡ Its beneficial action in this disease does not appear to be due solely to increased uric acid excretion, since the uricosuric action of the drug is not marked.§

There have been only a few studies of the effect of phenylbutazone on ocular inflammations. Some favorable reports were mentioned in last year's review. Intramuscular injection (local application was ineffective) of phenylbutazone was found to inhibit the inflammatory response to glycerin injected into the anterior chamber of the experimental animal as effectively as did cortisone.[301] The drug did not enter the aqueous humor in appreciable quantity. (This observation illustrates the interesting point that, other things being equal, penetration into the aqueous may not provide an index to the therapeutic potential of a drug.) Clinical studies have demonstrated phenylbutazone to be valuable in counteracting the inflammatory response in iritis, postoperative inflammation, and episcleritis.[302]

The initial oral adult dose of phenylbutazone is 600 mg. per day; the usual maintenance dose is 100 to 400 mg. per day. Phenylbutazone is quite toxic, its side-effects resembling those of cortisone in certain respects. Among these are sodium retention and activation and possible perforation of a peptic ulcer.[303] Agranulocytosis ascribed to phenylbutazone has been reported previously, and additional reports have appeared during the current year.‖ Other toxic manifestations include hypersensitivity (fatal), hepatitis, and acute renal failure.¶ The toxicity is of such proportions that therapeutic use of the drug is not advised, except under careful observation.

SEDATIVES AND HYPNOTICS

As mentioned in previous reviews, the barbiturates depress the activity of nerve tissue at multiple sites, including the motor cortex and the diencephalon. Work published during the past year demonstrated that the barbiturates variably depress the activity of the autonomic ganglia.[309] Among the various barbiturates, there appears to be little correlation between the degrees of depression of the ganglia and the central nervous system. The drop in blood pressure which may accompany barbiturate administration perhaps derives from this ganglionic action. A recent review of the distribution in the body and the metabolic fate of the barbiturates has appeared.[310] Specifically, studies of phenobarbital have demonstrated that this drug is eliminated slowly by man and that daily administration leads to an accumulation in the blood stream.[311] Tolerance to the hypnotic effects keeps pace with this accumulation and, consequently, untoward clinical effects are not usually noted. One dose daily of phenobarbital provides a relatively constant plasma level, and the authors suggest that there is little to gain by administering the drug more frequently.

† References 294 to 296.

‡ References 297 and 298.

§ References 299 and 300.

‖ References 304 and 305.

¶ References 306 to 308.

An experimental study of chronic barbiturate intoxication in man, using secobarbital in relatively large doses over a period of one to one and one-half months, demonstrated that the clinical manifestations of chronic intoxication were similar to those of chronic alcoholism.[312] Upon abrupt withdrawal, a definite abstinence syndrome appeared, the symptoms including weakness, tremor, anxiety, nausea and vomiting, and convulsions or psychosis.

Attention was directed again to the safety of thiopental sodium as an anesthetic for infants and children.[313]

A statistical study (conducted on ward patients admitted for elective surgery) demonstrated that the hypnotic effect of 0.5 to 1.0 gm. of methylparafynol (Dormison) was indistinguishable from that produced by a placebo. Chloral hydrate in doses of 1 gm. induced sleep more satisfactorily than did 0.1 gm. of pentobarbital sodium. A larger dose of pentobarbital (0.2 gm.) satisfactorily induced and maintained sleep for five or more hours. The barbiturate more frequently caused a "hang-over" than did chloral hydrate.[314]

THE LOCAL ANESTHETICS

The penetration of procaine into ocular tissues following subconjunctival injection has been studied in the experimental animal.[315] The salient conclusions from this study are (1) that such injection produces an appreciably higher concentration of procaine in the iris than in the aqueous, (2) that penetration of the drug is increased when epinephrine is added to the solution but is not substantially altered by hyaluronidase, and (3) that even under optimal conditions the resulting concentration of procaine in the iris is below, or barely within, the range required to produce anesthesia of small sensory nerves. If subconjunctival injection is to be used for surgical anesthesia of the iris, therefore, the authors recommend that vasoconstrictor drugs be included and that 5 to 10 minutes be allowed for the onset of anesthesia.

The search for agents which produce prolonged local anesthesia has led to a study comparing the effects of procaine, lidocaine, tetracaine, Efocaine (a preparation consisting of procaine, procaine hydrochloride, and butyl-*o*-aminobenzoate in a vehicle composed of polyethylene glycol, propylene glycol, and water, with sodium meta-bisulfite and phenylmercuric borate as preservatives), and a new agent identified as U-0045.[316] The anesthetic action of the last drug persists for 8 to 12 hours. In proper concentration, it was found to give safe and effective anesthesia. The anesthetic effect of tetracaine was not so prolonged as that of U-0045, but was considerably longer than that of either procaine or lidocaine. (Efocaine caused marked tissue reaction and is not recommended.) A solution of 2% ethyl aminobenzoate (Benzocaine) and 40% urethan is claimed to give prolonged local analgesia and to be free from irritant effect.[317] From such a solution, the ethyl aminobenzoate is precipitated in and slowly absorbed from tissues. Injection about the eye, however, was not studied.

For topical anesthesia a new agent has been described—benoxinate (Dorsacaine). In 0.4% aqueous solution it is less irritating than 0.5% tetracaine, while producing a more rapid and less prolonged anesthesia.[318]

Finally, it has been reported that a mixture of procaine and epinephrine (0.6 ml. of 4% procaine and 0.4 ml. of 1% epinephrine), given by retrobulbar injection, has an effective ocular hypotensive action and is recommended in ocular surgery for that reason.[319]

ANTIHISTAMINES AND CHEMICALLY RELATED DRUGS

An interesting review of some of the physiologic aspects of histamine has appeared.[320]

Little new is reported on either the ocular or the general pharmacology of the antihistamines. With certain exceptions, the clinical use of the drugs is directed at the inhibition of histamine. A study of the action of some of the antihistamines on the isolated iris musculature of the experimental animal has demonstrated their ability to counteract

the histamine-induced spasm of the sphincter. Certain antihistamines, themselves, induced a contraction of the sphincter.[321] It will be recalled that in general the antihistamines have an atropine-like action on the human iris and that in cases of toxicity from overdosage the pupil is dilated.

A relatively new drug, chlorpromazine, is chemically similar to, and has some of the actions of, certain of the antihistamines, but only slightly inhibits the tissue response to histamine. Chlorpromazine is a depressant drug and is mildly sedative, acting at certain sites in the brain stem, as well as at cortical and subcortical levels. The depressant action does not appear to be due to suppression of oxygen uptake.[322] Like some of the antihistamines, such as diphenhydramine, chlorpromazine effectively controls postoperative nausea and vomiting, as well as that which may occur in uremia, in radiation sickness, and in patients with carcinoma.* It does not prevent motion sickness, however.[327] The drug has been useful in the treatment of postoperative hiccups.[328] It is reported to enhance the analgesic effect of the opiate narcotics and the action of sedatives, actions which have led to its use in preoperative medication and in controlling pain from malignant disease[329] and in labor.[330] This effect is apparently due to an alteration of the patient's reaction to pain. Finally, chlorpromazine has been effective in the treatment of psychiatric diseases, including the psychoneuroses and certain psychotic states,† although its role here is still obscure.

Chlorpromazine has been little mentioned in literature devoted to ophthalmology. One publication has indicated that it may have merit in the treatment of glaucoma, particularly acute glaucoma[335]; unfortunately, no data were given in this report. The value of chlorpromazine as a preoperative medication in ocular surgery was also stressed.

Chlorpromazine is available for oral, intramuscular, and intravenous use. The parenteral dose varies from 10 to 25 mg. The usual oral dose ranges from 25 to 50 mg. four times daily, although higher doses may be employed. Side-effects of the drug include orthostatic hypotension,‡ tachycardia, and drowsiness. More serious is a hepatic toxicity, which may be fatal.[338] The clinical picture resembles that of an obstructive type of jaundice.§

VITAMINS

As pharmacologic agents, the vitamins have a definite value in the treatment of the deficiency state. In the well-nourished person, however, their clinical usefulness is not clearly established. For example, while deficiency of vitamin A leads to epithelial changes, an ophthalmic manifestation of which is xerophthalmia,[341] the metabolic contribution of this vitamin to the epithelium is not understood. Thus, it is difficult to credit reports that vitamin A is beneficial in certain diseases of epithelial structures, such as the skin and the cornea.

Nonetheless, the possibility exists that a disease may induce a vitamin deficiency at the cellular level. (A biochemical lesion must ultimately underlie most disease states.) One possible mechanism is suggested by a report of the development of a local motor neuropathy in the region of a carcinoma, due, apparently, to vitamin B (pyridoxine) deficiency, possibly resulting from a simple competition for the vitamin by the tumor and normal cells.[342] Too, a metabolic antagonist (a substance which, while chemically similar to the vitamin, does not fill its metabolic role[343]) may be produced by the diseased cell. Lastly, the diseased cell may have a higher vitamin requirement than the normal cell. In any event, high vitamin dosage is frequently claimed beneficial in certain disease conditions.‖ Such claims relative to the eye include reports that vitamin A[346] and nicotinic acid[347] aid in the healing of corneal ulcers.

Vitamin E has been demonstrated to be essential for the normal development of the eye in the turkey embryo. Turkey hens fed

* References 323 to 326.

† References 331 to 334.

‡ References 336 and 337.

§ References 339 and 340.

‖ References 344 and 345.

a diet deficient in vitamin E produced embryos with a central lens opacity and vitreal hemorrhage.[348] The human requirement of vitamin E is not known, however. Its use in the treatment of diabetic retinopathy has been suggested previously, but a study published during the year under review found it to be of no benefit.[349]

Vitamin B_{12} (cyanocobalamin U. S. P.) deserves special mention. This vitamin is essential for the prevention of certain megaloblastic anemias. It is poorly absorbed from the gastrointestinal tract of patients with pernicious anemia and those who have undergone total gastrectomy. In both cases, absorption of vitamin B_{12} is normalized when the intrinsic factor from the gastric mucosa is administered with the vitamin.¶ However, the quantity of vitamin B_{12} normally absorbed from the gastrointestinal tract is quite limited.# Ingestion of larger amounts of the vitamin does not appreciably increase the absorption.

Some studies have appeared to implicate vitamin B_{12} in the pathogenesis of diabetic retinopathy. These have included the observation that a larger portion of a test dose of vitamin B_{12} is excreted by a diabetic patient with retinopathy than by one without.[354] Likewise, Kimmelstiel-Wilson-like lesions are produced more readily by cortisone in experimental animals denied dietary vitamin B_{12}. Diabetic retinopathy, however, is not a manifestation of vitamin deficiency, as the term is usually understood. Actually, the serum level of vitamin B_{12} in patients with diabetic retinopathy is reported to be considerably higher than in diabetics without retinal manifestations.[355] Whatever the significance of this observation, it is clear that the administration of vitamin B_{12} has not been beneficial in the treatment of diabetic retinopathy.[356]

A pigmentary degeneration of the retina of experimental animals reportedly responds to vitamin B_{12}.[357]

The vitamins which are most likely to be toxic on excessive ingestion are the fat-soluble vitamins, A and D. Chronic overdose of vitamin D may, because of the increased calcium retention, cause deposits of calcium in the cornea, leading to a band keratopathy. The condition is reversible.[358]

¶ References 350 and 351.

References 352 and 353.

ENZYMES

Hyaluronidase, the so-called "spreading factor," is that enzyme which depolymerizes hyaluronic acid and reduces the viscosity of its solution. Physiologically, the enzyme increases the rate of dissemination of substances injected into the skin and other tissues.

The effect of hyaluronidase on the ocular structures has been reexamined during the past year. One study demonstrated that in the doses employed the enzyme does not promote the absorption of blood from the vitreous of the rabbit.[359] Another study showed the injection of hyaluronidase into the anterior chamber to be well tolerated by rabbit eyes.[360] These results differ from those of previous workers, who found the enzyme to be locally toxic. The weight of evidence favors the view that the intraocular use of hyaluronidase may be dangerous and has no therapeutic merit.

Streptokinase, an enzyme isolated from streptococci, reacts with a plasma constituent to form a fibrinolytic enzyme. The injection of 10,000 units or less of the enzyme into the anterior chamber of the rabbit is said to produce no local toxic reaction. In such amounts, however, it does not promote the absorption of blood from the aqueous.[361] Another study demonstrated that streptokinase activity in the aqueous decreases rapidly after injection of the enzyme into the anterior chamber, that the fibrinolytic activity can be prolonged by the intracameral injection of a mixture of plasma and enzyme, but that the clearing time of a hyphema is only slightly reduced following injection of the streptokinase into the anterior chamber of the rabbit.[362] These and previous studies indicate that intraocular injection of streptokinase is of no value in ophthalmic practice.

However, a mixture of streptokinase and streptodornase, the latter being the enzyme

which lyses nuclear debris, appears helpful in the treatment of purulent corneal ulcers. The enzymes are applied topically in combination with antibiotic therapy, and, by removing fibrin and cellular debris, assist the healing of the ulcers.[363]

Trypsin is a proteolytic enzyme which promotes the hydrolysis of fibrin, as well as cellular debris. Intravenous administration of trypsin to lyse clots has been recommended in the past. Such use of the enzyme, however, does not alter artificially induced intravascular thrombi, and there appears to be insufficient evidence to justify the intravenous use of trypsin to lyse intravascular clots.[364] The intravenous administration of trypsin in two cases of thrombosis of the central retinal vein reportedly failed to produce any clear-cut evidence of benefit.[365]

There are reports, however, that the intramuscular administration of a crystalline trypsin preparation in a sesame oil vehicle (Parenzyme) may alter the course of thrombophlebitis favorably, supposedly by activating a fibrinolytic system.[366] Studies with experimental animals have suggested that intramuscular injection of trypsin or other proteolytic enzymes may exert a general anti-inflammatory effect, as evidenced by their ability to inhibit the formation of edema by egg white.[367] The formation of granulation tissue (measured by the granuloma pouch technique) was not altered by the intramuscular injection of the enzyme at a distant site.[368] On the other hand, injection of a mixture of trypsin and chemical irritant (croton oil) into a granuloma pouch causes a more widespread and intense tissue damage than injection of the irritant only.[369] Such anti-inflammatory action as this method of injection may have appears, then, to result from some factor other than the delivery of trypsin to the inflamed site. The evidence that the intramuscular use of trypsin may be of value in ophthalmology is not conclusive.

RADIOACTIVE ISOTOPES

The diagnostic use of radioactive isotopes about the eye has been limited to detection of malignant growths. For this purpose, a small amount of radioactive phosphorus (P^{32}) is injected intravenously and the radioactivity over the site of the tumor subsequently measured, comparing it with the activity at an unaffected site of the same or the other eye. (A curved scintillation counter has been devised for investigating lesions in the posterior segment of the eye.[370]) A higher count should be obtained over the tumor, due to its preferential uptake of P^{32}. This may result either from the increased vascularity of the tumor or from the accelerated metabolic integration of phosphorus into its highly active cells. The problem of distinguishing between an inflammatory and a malignant lesion is thus troublesome. In general, the results have demonstrated that the radioactive-isotope technique provides a fairly reliable indication of malignancy,* although there are differences of opinion regarding the criteria for considering a pathologic process malignant. Reports of failure in detecting subsequently proved malignant lesions have appeared, however.[375] The weight of present evidence indicates that the technique is valuable as an adjunct to the usual clinical studies.

Certain radioactive isotopes are useful in the therapy of tissues which, because of some metabolic or physiologic peculiarity, preferentially accumulate those isotopes. Examples of such therapy include the depression of thyroid activity with radioactive iodine,† the treatment of polycythaemia rubra vera with P^{32},[378] and the treatment of carcinomatosis of serous body cavities with radioactive colloidal gold.[379] No similar therapy has been found for ocular disease.

Radioactive isotopes also are used to deliver contact or air-borne radiant energy. For such application, the gamma and the beta rays are clinically useful. The former are equivalent in biological effect to the higher-energy x-rays and, consequently, are more useful in deep therapy. Aside from radium, the gamma-ray emitter used most

* References 371 to 374.

† References 376 and 377.

is radioactive cobalt (Co^{60}).[389] It is used for intracavitary therapy and for replacing x-rays in teletherapy.

The beta rays are particulate (i. e., electrons), and their tissue penetration is considerably less than that of gamma rays. The isotopes commonly employed for their beta-ray emanation are radioactive strontium (Sr^{90}), radon and other radium-disintegration products, and, less frequently, P^{32}. The exact depth of tissue penetration of the energy depends upon the isotope, but is generally less than 1 mm. and, thus, is comparable to low-voltage x-rays. Such radiation benefits only superficial lesions. The successful treatment of carcinoma at the limbus with Sr^{90},[381] and inhibition of corneal vascularization with low-voltage x-rays[382] have been reported. Other uses were mentioned in past reviews.

In spite of low penetration, however, the use of beta rays or low-voltage x-rays about the eye has its hazards. Such radiation penetrates sufficiently deep to cause cataract,[383] the lens being particularly vulnerable to radiation applied over the limbus.[384] A further study has indicated that the simultaneous irradiation of both the ciliary body and the lens causes a more rapid and complete cataractous change than irradiation of the lens only.[385]

No single metabolic or biochemical lesion appears to account for the many cellular disturbances which such radiant energy induces. An informative discussion of this subject has been published during the current year.[386] Interesting observations have indicated that hypoxia affords protection against x-ray injury,[387] and, on the other hand, that x-irradiation may protect against oxygen poisoning.[388]

Reportedly, energy in the visible or short infrared range released by an atomic bomb may produce a retinal burn not unlike eclipse blindness in a person looking toward the explosion.‡

‡ References 389 and 390.

THE ANTIMALIGNANT AGENTS

The most commonly used antimalignant agents are the nitrogen mustards and triethylenemelamine. A recent comprehensive review of the biologic actions of the nitrogen mustards and their therapeutic use is available.[391] The antimalignant action of these agents probably stems from their inhibition of cell division. This inhibition is only temporary and, in experimental situations, is eventually circumvented by the cell, even though the concentration of nitrogen mustard is maintained.[392] This mirrors clinical experience, wherein these drugs, which are initially quite active against such malignant tumors as the lymphomas, eventually lose their effectiveness. The nitrogen mustards have numerous metabolic effects, including the stimulation of glycolysis[393] and the inhibition of nucleic acid synthesis, but no close parallel appears between their metabolic effects and their ability to inhibit cellular division.[394]

ANTICOAGULANTS

The systemically used anticoagulants fall into two main groups. The first is exemplified by heparin, which interferes with the conversion of prothrombin to thrombin. Heparin is a polysaccharide sulfate; other compounds of similar structure also have anticoagulant action.[395] Intravenously administered heparin disappears quite rapidly from the blood stream. Subcutaneous injection prolongs the anticoagulant effect. Apparently, heparin is produced by the mast cell and is found in high concentration in mast cell tumors.[396]

Heparin has certain physiologic effects which are probably unrelated to its anticoagulant ability. These include the accelerated clearing of lipemia after a fat meal and the alteration of the plasma lipid pattern in normal and atherosclerotic persons.[397] There are an associated alteration of the lipoprotein complexes[398] and an increase in free fatty acids, suggesting a lipolysis.[399] Perhaps related is the clearing of xanthalasma by local heparin injection. Heparin blocks the Shwartzman reaction, an activity

not generally shared by the anticoagulant agents which induce hypoprothrombinemia.§ The polysaccharide also blocks the development of experimental nephrosis in rats administered antikidney serum.[402] Other actions include a degree of anticortisone activity.

The other group of anticoagulant drugs is comprised of those antimetabolites of vitamin K_1 which inhibit the formation of prothrombin. It includes the coumarin compounds and newer agents, such as phenindione (phenylindanedione). They are effective when administered orally. The major difference between the various drugs of this group lies in the rate of their induction of the hypoprothrombinemia and in its duration.‖ The hypoprothrombinemia induced by bishydroxycoumarin (Dicumarol) develops later and endures longer than that caused by ethyl biscoumacetate (Tromexan) or phenylindanedione. Overdosage of these drugs causes a hemorrhagic tendency, to which vitamin K_1 is thought to be antidotal.[405] Drug sensitivity to phenylindanedione has been reported,[406] a toxic effect distinct from its anticoagulant effect.

Neither heparin nor those agents which cause a hypoprothrombinemia dissolve thrombi, and, in theory, their therapeutic usefulness would be limited to the prevention of thrombus formation or extension. Experimental work has indicated that the two groups of anticoagulants vary in ability to prevent a chemically produced thrombosis in animals. Ethyl biscoumacetate seems quite effective in this role, whereas heparin affords no protection.[407]

Opinion varies concerning the value of the anticoagulants in the treatment of coronary occlusion or cerebrovascular disturbances deemed thrombotic.¶ Their merit in treatment of acute vascular accidents in the eye is questionable. Persons with a retinal venous thrombosis are reported to show no significant alteration of blood coagulability, as measured by the usual laboratory procedures.[411] Anticoagulant treatment of venous thrombosis of the retina appears to have no particular merit. Bishydroxycoumarin has been reported to be of value in the treatment of retinitis pigmentosa.[412]

§ References 400 and 401.

‖ References 403 and 404.

¶ References 408 to 410.

FIBRIN

In certain corneal diseases, particularly corneal ulcerations, the deposition of a fibrin film is claimed to afford more comfort and to increase the rate of healing.# The formation of a fibrin film requires fibrinogen and thrombin. Certain poly-α-amino acids accelerate the conversation of fibrinogen to fibrin by thrombin and thereby promote the clotting of fibrinogen in concentrations too low to clot otherwise.[413]

PHARMACEUTICAL ASPECTS OF OPHTHALMIC AGENTS AND THEIR METHOD OF ADMINISTRATION

A study of the stability of drugs employed in the treatment of glaucoma has indicated that the pH of aqueous solutions of salts of pilocarpine, physostigmine, carbachol, methacholine, and neostigmine shows little change over 10 to 11 months.[416] In general, the physiologic activity of the solutions is fairly well maintained during this time period. Bisulfite is often added as a preservative to prevent deterioration and thus increase the shelf life of ophthalmic solutions.

The maintenance of sterility of ophthalmic solutions during continued use presents a difficult problem. Bacterial contamination of the common dropper bottle probably occurs frequently, constituting a definite hazard, particularly in certain solutions.[417] Of the various drugs added to maintain sterility, chlorobutanol in 0.5% solution appears to be a good all-purpose agent.[418] Others, such as phenylmercuric nitrate (0.005%), are also useful. The bactericidal agent used might best vary with the solution.[419]

Experimental and clinical studies of the various ointment bases for ophthalmic preparations have demonstrated that a mixture

References 413 and 414.

of 80% petrolatum (Vaseline) and 20% liquid petrolatum is a useful vehicle.[420] For a water-soluble drug, these authors recommend that cetyl alcohol, in sufficient quantity to provide a concentration of 5%, be used as an emulsifier.

Mention should be made of the administration of drugs by iontophoresis. This technique is, of course, applicable only to salts. To the eye is applied the pole whose charge is the same as the ion being used for treatment. A unit which can be used for both iontophoresis and electrolysis has been described.[421] The successful clinical administration by iontophoresis of such drugs as the sulfonamides, antibiotics, and methacholine has been reported. This report also claimed that iontophoresis of calcium and physostigmine cleared a cloudy vitreous and that the degree of amblyopia was reduced following iontophoresis of vasodilators, e. g., physostigmine and acetylcholine, into the eye.[422]

TOXICOLOGY

During the past year, studies of the toxic effects of methanol on the optic nerve and retina were reported. Included were three papers* from one laboratory, from which the following conclusions were drawn: First, among experimental animals, only primates respond to methanol similarly to man. (One of the major handicaps in studying this problem has been that of finding a suitable experimental animal.) Second, studies with monkeys have indicated that, although sodium bicarbonate may prevent fatality from methanol, a treatment which has been well established in man, retinal changes may, nonetheless, occur. These include a perimacular edema, followed by a more generalized edema of the retina and, lastly, a papilledema. Regression of these changes occurs in the reverse order. Third, studies of the electroretinogram in experimental animals substantiate the authors' original postulation that in methanol poisoning formaldehyde is the agent ultimately toxic to the retina.

* References 423 to 425.

Electroretinographic studies in quinine poisoning demonstrated that shortly after the onset of visual disturbance, when visual symptoms and signs were severest, the ERG was unaltered. Somewhat later, when the visual status and the fundus picture had improved, the b-wave potential was lowered.[426] Visual symptoms resulting from digitalis overdose have been reported as well.[427] Their cause is obscure. Discontinuation of the digitalis leads to return of vision, with no permanent impairment.

The toxic effects of substances which may cause a hypercalcemia have been alluded to under the discussion of vitamins, where it was mentioned that a high vitamin D intake may lead to a band keratopathy. This has been described also in a woman who died of acute parathyroid poisoning.[428] In this instance, generalized deposits of calcium in the sclera, conjunctiva, and cornea were noted and fundus changes were seen also.

Successful removal of calcium from the cornea with ethylenediaminetetraacetic acid has been described in previous years and was again reported during the year under review.[429] This compound forms with calcium a relatively undissociated, but water-soluble, salt. Given systemically in sufficient quantity, it may evoke a calcium deficiency. Its use is recommended in the treatment of lime burns of the eye.[430]

REFERENCES

1. McCann, S. M., and Brobeck, J. R.: Evidence for a Role of the Supraopticohypophyseal System in Regulation of Adrenocorticotrophin Secretion, Proc. Soc. Exper. Biol. & Med. **82**:318-324 (Nov.) 1954.

2. McCann, S. M., and Sydnor, K. L.: Blood and Pituitary Adrenocorticotrophin in Adrenalectomized Rats with Hypothalamic Lesions, Proc. Soc. Exper. Biol. & Med. **82**:369-373 (Nov.) 1954.

3. Paris, J.; Upson, M., Jr.; Sprague, R. G.; Salassa, R. M., and Albert, A.: Corticotropic Activity of Human Blood, J. Clin. Endocrinol. **14**:597-607 (June) 1954.

4. Rubin, B. L.; Dorfman, R. I., and Dorfman, A.: Adrenocorticotropic Hormone (ACTH) in Urine, J. Clin. Endocrinol. **14**:154-160 (Feb.) 1954.

5. Macchi, I. A., and Hechter, O.: Studies of ACTH Action upon Perfused Bovine Adrenals: Minimal ACTH Concentration Requisite for Maximal Glandular Response, Endocrinology **55**:426-433 (Oct.) 1954.

6. Macchi, I. A., and Hechter, O.: Studies of ACTH Action upon Perfused Bovine Adrenals: Duration of ACTH Action, Endocrinology **55**:434-438 (Oct.) 1954.

7. Rauschkolb, E. W.; Rosnagle, R. S., and Farrell, G. L.: Secretion of 17-Hydroxycorticosterone by Adrenal of Hypophysectomized Dog: Effect of ACTH, Proc. Soc. Exper. Biol. & Med. **86**:785-787 (Aug.-Sept.) 1954.

8. Sweat, M. L., and Farrell, G. L.: Decline of Corticosteroid Secretion Following Hypophysectomy, Proc. Soc. Exper. Biol. & Med. **87**:615-618 (Dec.) 1954.

9. Collins, E. J., and Olson, K. J.: Inhibition of Steroid-Induced Adrenal Hypofunction, Proc. Soc. Exper. Biol. & Med. **87**:76-78 (Oct.) 1954.

10. Farrell, G. L.; Royce, P. C.; Rauschkolb, E. W., and Hirschmann, H.: Isolation and Identification of Aldosterone from Adrenal Venous Blood, Proc. Soc. Exper. Biol. & Med. **87**:141-143 (Oct.) 1954.

11. Swingle, W. W.; Ben, M.; Maxwell, R.; Baker, C.; Fedor, E., and Barlow, G.: Effect of the Sodium-Retaining Factor of the Adrenal Cortex upon the Serum Electrolytes of Adrenalectomized Dogs, Endocrinology **54**:698-705 (June) 1954.

12. Swingle, W. W.; Maxwell, R.; Ben, M.; Baker, C.; LeBrie, S. J., and Eisler, M.: Effect of Aldosterone and Desoxycorticosterone on Adrenalectomized Dogs, Proc. Soc. Exper. Biol. & Med. **86**:147-150 (May) 1954.

13. Selye, H.: Anticortisol Action of Aldosterone, Science **121**:368-369 (March 11) 1955.

14. Hechter, O., and Pincus, G.: Genesis of the Adrenocortical Secretion, Physiol. Rev. **34**:459-496 (July) 1954.

15. Kinsell, L. W.; Michaels, G. D.; Margen, S.; Partridge, J. W.; Boling, L., and Balch, H. E.: The Case for Cortical Steroid Hormone Acceleration of Neoglucogenesis from Fat in Diabetic Subjects: A Summary of 5 Years' Investigative Work, J. Clin. Endocrinol. **14**:161-176 (Feb.) 1954.

16. Timiras, P. S.; Woodbury, D. M., and Goodman, L. S.: Effect of Adrenalectomy, Hydrocortisone Acetate and Desoxycorticosterone Acetate on Brain Excitability and Electrolyte Distribution in Mice, J. Pharmacol. & Exper. Therap. **112**: 80-93 (Sept.) 1954.

17. Breibart, S., and Engel, F. L.: Influence of Cortisone and Insulin on the Respiratory Activity of Rat Adipose Tissue in Vitro, Endocrinology **55**:70-76 (July) 1954.

18. Sobel, H., and Marmorston, J.: Effect of Cortisone on the Collagen and Hexosamine Content of the Skin and Femurs of One Year Old Rats, Endocrinology **55**:21-27 (July) 1954.

19. Loxton, G. E., and LeVay, D.: A Method of Studying the Modification by Drugs of the Oxidation-Reduction Systems of the Skin, J. Pharm. & Pharmacol. **6**:178-186 (March) 1954.

20. Long, D. A.: Influence of Cysteinamine on Tuberculin Sensitivity in Guinea-Pigs, Brit. J. Pharmacol. **9**:118-120 (March) 1954.

21. Essellier, A. F.; Jeanneret, P.; Kopp, E., and Morandi, L.: Evidence Against Destruction of Eosinophils by Glucocorticoids As Shown by in Vitro Experiments, Endocrinology **54**:477-479 (April) 1954.

22. Miller, Z.: A Study of the Lymphocytolytic Action of an Adrenal Cortical Extract in Vitro, Endocrinology **54**:431-436 (April) 1954.

23. Shulman, M. H.; Fulton, G. P., and Moront, G. P.: Effect of Cortisone on the Healing of Localized Burns in the Hamster Cheek Pouch, New England J. Med. **251**:257-261 (Aug. 12) 1954.

24. Rosenman, R. H.; Freed, S. C., and Smith, M. K.: Effect of Cortisone upon Vascular Responsiveness of Potassium-Deficient and Normal Rats, Proc. Soc. Exper. Biol. & Med. **87**:292-295 (Nov.) 1954.

25. von Sallmann, L.; Pillat, B., and Powers, M. M.: Influence of ACTH and Cortisone on the Reactivity of the Terminal Vascular Bed in the Eye, Am. J. Ophth. **38**:122-134 (July, Pt. II) 1954.

26. von Sallmann, L.; Pillat, B., and Powers, M. M.: Further Studies on the Influence of ACTH on the Reactivity of the Terminal Vascular Bed in the Eye, Am. J. Ophth. **38**:655-669 (Nov.) 1954.

27. Harris, H.: Role of Chemotaxis in Inflammation, Physiol. Rev. **34**:529-562 (July) 1954.

28. Grossfeld, H., and Ragan, C.: Action of Hydrocortisone on Cells in Tissue Culture, Proc. Soc. Exper. Biol. & Med. **86**:63-68 (May) 1954.

29. Sigelman, S.; Dohlman, C. H., and Friedenwald, J. S.: Mitotic and Wound-Healing Activities in the Rat Corneal Epithelium, A. M. A. Arch. Ophth. **52**:751-757 (Nov.) 1954.

30. Halberg, F., and Spink, W. W.: Maintenance of Physiologic Temperatures by Halogenated Corticoid in Adrenalectomized Mice Given Brucella Somatic Antigen, Proc. Soc. Exper. Biol. & Med. **88**:222-223 (Feb.) 1955.

31. Leathem, J. H., and Wolf, R. C.: Life Maintaining Action of 9 Alpha Chlorohydrocortisone Acetate in Adrenalectomized Rats, Proc. Soc. Exper. Biol. & Med. **86**:724-725 (Aug.-Sept.) 1954.

32. Borman, A.; Singer, F. M., and Numerof, P.: Growth-Survival and Sodium Retaining Activity of 9α-Halo Derivatives of Hydrocortisone, Proc. Soc. Exper. Biol. & Med. **86**:570-573 (July) 1954.

33. Swingle, W. W.; Baker, C.; Eisler, M.; LeBrie, S. J., and Brannick, L. J.: Efficacy of 9 Alpha-Halo Adrenal Steroids for Maintenance of Adrenalectomized Dogs, Proc. Soc. Exper. Biol. & Med. **88**:193-196 (Feb.) 1955.

34. Herzog, H. L.; Nobile, A.; Tolksdorf, S.; Charney, W.; Hershberg, E. B., and Perlman, P. L.: New Antiarthritic Steroids, Science **121**:176 (Feb. 4) 1955.

35. Bunim, J. J.; Pechet, M. M., and Bollet, A. J.: Studies on Metacortandralone and Metacortandracin in Rheumatoid Arthritis, J. A. M. A. **157**:311-318 (Jan. 22) 1955.

36. Benjamin, F. B., and Cornbleet, T.: Effect of Local Adrenocortical Hormones on Cutaneous Spreading, A. M. A. Arch. Dermat. & Syph. **70**: 483-487 (Oct.) 1954.

37. Zacco, M.; Richardson, E. M.; Crittenden, J. O.; Hollander, J. L., and Dohan, F. C.: Disposition of Intra-Articularly Injected Hydrocortisone Acetate, Hydrocortisone and Cortisone Acetate in Arthritis: I. Concentrations in Synovial Fluid and Cells, J. Clin. Endocrinol. **14**:711-718 (July) 1954.

38. Green, H., and Leopold, I. H.: Investigation of Corticosteroids in the Aqueous Humor of Normal Animal Eyes, Am. J. Ophth. **38**:101-106 (July, Pt. II) 1954.

39. Lepri, G., and Montanari, L.: L'Action de l'hormone corticotrope (ACTH) sur le contenu en corticoides de l'humeur aqueuse de première et de seconde extraction, Ophthalmologica **127**:110-112 (Feb.) 1954.

40. Weimar, V. L., and Leopold, I. H.: Intraocular Penetration of Local Hydrocortisone and Cortisone, A. M. A. Arch. Ophth. **52**:769-773 (Nov.) 1954.

41. Sandberg, A. A.; Eik-Nes, K.; Nelson, D. H.; Palmer, J. G.; Cartwright, G. E., and Wintrobe, M. M.: Adrenocortical Function and Metabolism of 17-Hydroxycorticosteroids in Pernicious Anemia, New England J. Med. **251**:169-174 (July 29) 1954.

42. Bacchus, H.: Maintenance of Blood 17-Hydroxycorticosteroids Following Ascorbic Acid Treatment, Endocrinology **54**:402-408 (April) 1954.

43. Hogan, M. J.; Thygeson, P., and Kimura, S.: Uses and Abuses of Adrenal Steroids and Corticotropin, A. M. A. Arch. Ophth. **53**:165-176 (Feb.) 1955.

44. Gordon, D. M.: Hydrocortisone in Ophthalmology, Am. J. Ophth. **37**:533-538 (April) 1954.

45. Dernoncourt: Comment Conduire un Traitement par la cortisone ou l'A.C.T.H., Ann. ocul. **187**:551-560 (June) 1954.

46. Lugossy, G., and Takats, E.: Erfahrungen mit Cortison, Klin. Monatsbl. Augenh. **125**:749-755 (Nov.-Dec.) 1954.

47. Pereira, R. F.: El Uso de la cortisona en oftalmologia, Arch. oftal. Buenos Aires **29**:29-37 (Jan.) 1954.

48. von Stark, H.: Cortison und Auge: Ein klinischer Erfahrungsbericht: I. Mitteilung, Klin. Monatsbl. Augenh. **124**:96-101, 1954.

49. Stark, H.: Cortison und Auge: II. Mitteilung, Klin. Monatsbl. Augenh. **124**:584-590, 1954.

50. Horne, G. O.: Topical Cortisone in the Treatment of Syphilitic Interstitial Keratitis, Brit. J. Ophth. **38**:669-672 (Nov.) 1954.

51. North, D. P.: Treatment of Interstitial Keratitis, Brit. M. J. **2**:7-9 (July 3) 1954.

52. Sie-Boen-Lian, and Oey-Khoen-Lian: Results of Cortisone Administration in Keratitis Interstitialis and Westhoff's Keratitis, Ophthalmologica **127**:414-418 (June) 1954.

53. Rouher, M. F.: Hydrocortisone et eczema atropinique, Bull. Soc. opht. France, pp. 200-205, February, 1954.

54. Scheie, H. G., and Alper, M. C.: Treatment of Herpes Zoster Ophthalmicus with Cortisone or Corticotropin, A. M. A. Arch. Ophth. **53**:38-44 (Jan.) 1955.

55. Israel, H. L.; Sones, M., and Harrell, D.: Cortisone Treatment of Sarcoidosis: Experience with 36 Cases, J. A. M. A. **156**:461-466 (Oct. 2) 1954.

56. Freeman, I.: Cortisone Treatment of Ocular Palsy in Sarcoidosis, Ann. Int. Med. **40**:356-361 (Feb.) 1954.

57. Gurling, K. J.; Bruce-Pearson, R. S., and Pond, M. H.: Sjögren's Syndrome Treated with ACTH, Brit. J. Ophth. **38**:619-625 (Oct.) 1954.

58. Reymann, F., and Sobye, P.: Follow-Up of Pemphigus Patients Treated with ACTH, Acta dermat.-venereol. **34**:152-158, 1954.

59. Barrios, R. M.; Malamud, B., and Arbo, J. M.: Un Caso de penfigo ocular tratado con cortisona y ACTH, Arch. oftal. Buenos Aires **29**: 329-335 (June) 1954.

60. Mauriello, D. A.: Erythema Multiforme Exudativum (Stevens-Johnson Syndrome) J. A. M. A. **156**:1495-1498 (Dec. 18) 1954.

61. Arata, A. F., and Pianciola, A. C.: Manifestaciones oculares del sindrome Stevens-Johnson, Arch. oftal. Buenos Aires **29**:555-567 (Nov.) 1954.

62. Bain, W. E., and Hobbs, H. E.: A Further Report on the Response of Macular Disease to Treatment with Cortisone and ACTH, Proc. Roy. Soc. Med. **47**:722-730 (Sept.) 1954.

63. Smelser, G. K., and Ozanics, V.: Further Studies on the Nature of the Exophthalmos-Producing Principles in Pituitary Extracts, Am. J. Ophth. **39**:146-155 (Feb., Pt. II) 1955.

64. Bennett, J. E.: Periodic Unilateral Exophthalmos, A. M. A. Arch. Ophth. **52**:683-698 (Nov.) 1954.

65. Rubin, I. L., and Billet, E.: Treatment of Malignant Exophthalmos with ACTH and Cortisone, New York J. Med. **54**:2991-2992 (Nov. 1) 1954.

66. Unger, L., and Unger, A.: Use and Abuse of Corticotropin (ACTH) and Cortisone in Allergic Conditions, Ann. Int. Med. **40**:721-728 (April) 1954.

67. Lincoln, M., and Ricker, W. A.: A Case of Periarteritis Nodosa with L. E. Cells: Apparent Complete Remission with Cortisone Therapy, Ann. Int. Med. **41**:639-646 (Sept.) 1954.

68. Anderson, A. E., Jr.: Suppression of the Manifestations of Gout with Continuous Cortisone Therapy, Am. J. Med. **16**:292-294 (Feb.) 1954.

69. Massell, B. F.: ACTH and Cortisone Therapy of Rheumatic Fever and Rheumatic Carditis, New England J. Med. **251**:183-190 (July 29); 221-228 (Aug. 5), and 263-270 (Aug. 12) 1954.

70. Leinwand, I.; Duryee, A. W., and Richter, M. N.: Scleroderma (Based on a Study of over 150 Cases), Ann. Int. Med. **41**:1003-1041 (Nov.) 1954.

71. Heilesen, B.; Kristjansen, A., and Reymann, F.: Hydrocortisone in Therapy of Cutaneous Disease, A. M. A. Arch. Dermat. & Syph. **70**:360-362 (Sept.) 1954.

72. Sulzberger, M. B., and Witten, V. H.: Prolonged Therapy with Cortisone for Chronic Skin Diseases, J. A. M. A. **155**:954-959 (July 10) 1954.

73. Robinson, H. M., Jr., and Robinson, R. C. V.: Treatment of Dermatoses with Local Application of Hydrocortisone Acetate, J. A. M. A. **155**:1213-1216 (July 31) 1954.

74. Report by the Joint Committee of the Medical Research Council and Nuffield Foundation on Clinical Trials of Cortisone, A. C. T. H., and Other Therapeutic Measures in Chronic Rheumatic Diseases: A Comparison of Cortisone and Aspirin in the Treatment of Early Cases of Rheumatoid Arthritis, Brit. M. J. **1**:1223-1227 (May 29) 1954.

75. Houser, H. B.; Clark, E. J., and Stolzer, B. L.: Comparative Effects of Aspirin, ACTH and Cortisone on the Acute Course of Rheumatic Fever in Young Adult Males, Am. J. Med. **16**:168-180

76. Calamendrei, M. G.: Inconvénients et dangers d'un usage indiscriminé de la cortisone en ophtalmologie, Bull. Soc. opht. France, pp. 465-472, June, 1954.

77. Offret, G., and Massin, M.: L'Administration locale de cortisone peut-elle être dangereuse en ophtalmologie?, Bull. Soc. opht. France, pp. 212-216, March, 1954.

78. François, J.: Cortisone et tension oculaire, Ann. ocul. **187**:805-816 (Sept.) 1954.

79. Laval, J., and Collier, R., Jr.: Elevation of Intraocular Pressure Due to Hormonal Steroid Therapy in Uveitis, Am. J. Ophth. **39**:175-182 (Feb.) 1955.

80. Holland, R. W., and Lepisto, V. E.: Cortisone and Neosone in Complications Following Cataract Surgery, Am. J. Ophth. **38**:201-203 (Aug.) 1954.

81. Yasuna, J. M.; Ojers, G. W.; Frayer, W. C., and Schele, H. G.: An Experimental Study of the Effect of Cortisone on the Eye, Am. J. Ophth. **37**:923-931 (June) 1954.

82. Daugherty, J. W.; Reisch, M., and Lewis, G. M.: Lowered Resistance to Infection Resulting from Cortisone and Corticotropin, New York J. Med. **54**:2964-2967 (Nov. 1) 1954.

83. Mankowski, Z. T., and Littleton, B. J.: Action of Cortisone and ACTH on Experimental Fungus Infections, Antibiotics & Chemother. **4**: 253-258 (March) 1954.

84. Havsky, J., and Foley, E. J.: Studies on the Effect of Cortisone with Chemotherapeutic Agents on Tuberculous Peritonitis in Mice, Antibiotics & Chemother. **4**:1068-1074 (Oct.) 1954.

85. Davis, M. E., and Plotz, E. J.: Effects of Cortisone Acetate on Intact and Adrenalectomized Rats During Pregnancy, Endocrinology **54**:384-395 (April) 1954.

86. Fraser, F. C.; Kalter, H.; Walker, B. E., and Fainstate, T. D.: Experimental Production of Cleft Palate with Cortisone and Other Hormones, J. Cell. & Comp. Physiol. **43**:237-259 (May) 1954.

87. Katzenstein, L., and Morris, A. J.: Cortisone and ACTH in Pregnancy, New England J. Med. **250**:366-367 (March 4) 1954.

88. Loh, W. P., and Street, R. B., Jr.: Study of the Use of Antimicrobial Agents in a Community Hospital, New England J. Med. **251**:659-660 (Oct. 14) 1954.

89. Paine, T. F., and Clark, L. S.: Effects of Streptomycin on Resting Suspensions of Escherichia Coli Grown on Three Carbon Sources, Antibiotics & Chemother. **4**:262-265 (March) 1954.

90. Maxwell, R. E., and Nickel, V. S.: Antibacterial Activity of the Isomers of Chloramphenicol, Antibiotics & Chemother. **4**:289-295 (March) 1954.

91. Hopps, H. E.; Wisseman, C. L., Jr., and Hahn, F. E.: Mode of Action of Chloramphenicol: V. Effect of Chloramphenicol on Polysaccharide Synthesis by Neisseria Perflava, Antibiotics & Chemother. **4**:857-858 (August) 1954.

92. Esplin, D. W., and Marcus, S.: Relation Between Antibacterial Action of Penicillin and Mouse Host Defenses in Systemic Pneumococcus Infection, Antibiotics & Chemother. **4**:423-432 (April) 1954.

93. Metzger, J. F.; Fusillo, M. H.; Roerig, R. N., and Ernst, K. F.: Phage Typing of Antibiotic-Resistant Staphylococci: III. Infection, Cross-Infection and Superinfection, New England J. Med. **250**:1030-1033 (June 17) 1954.

94. Berntsen, C. A., Jr.: Unaltered Penicillin Susceptibility of Streptococci: Study of Alpha Hemolytic Streptococci Causing Endocarditis, 1944 to 1954, J. A. M. A. **157**:331-333 (Jan. 22) 1955.

95. Hopps, H. E.; Wisseman, C. L., Jr., and Whelan, J.: Relation of Antibiotic Resistance of Staphylococci to Prevalence of Antibiotic Therapy in Diverse Geographic Areas, Antibiotics & Chemother. **4**:270-276 (March) 1954.

96. Dowling, H. F.; Lepper, M. H., and Jackson, G. G.: Clinical Significance of Antibiotic-Resistant Bacteria, J. A. M. A. **157**:327-331 (Jan. 22) 1955.

97. Hausler, H. R., and Ormsby, H. L.: Penetration of Magnamycin into the Aqueous Humor of Rabbits, Am. J. Ophth. **39**:234-241 (Feb., Pt. II) 1955.

98. Hummelt, K.: Untersuchungen über das Verhalten der Blut-KammerwasserSchranke gegenüber radioaktivem Penicillin nach intramuskularer Injektion bei Kaninchen, Klin. Moratsbl. Augenh. **124**:154-158, 1954.

99. Davson, H.: Permeability in the Mammal (with Special Reference to the Intra-Ocular Fluid), Acta physiol. et pharmacol. neerl. **3**:553-574 (Dec.) 1954.

100. Hall, B.: Absorption and Distribution of Aureomycin in Man: A Review of the Literature and Study of the Concentration of Aureomycin in the Serum, Urine and Cerebrospinal Fluid After Oral Administration, Ann. Int. Med. **40**:743-754 (April) 1954.

101. Wood, W. S.; Kipnis, G. P.; Spies, H. W.; Dowling, H. F.; Lepper, M. H., and Jackson, G. G.: Tetracycline Therapy, A. M. A. Arch. Int. Med. **94**:351-363 (Sept.) 1954.

102. Montmorency, F. A.; Caffery, E. L., and Musselman, M. M.: Observation on the Use of Oxytetracycline Intramuscularly, Antibiotics & Chemother. **4**:313-318 (March) 1954.

103. Waddington, W. S.; Smart, T. B., and Kirby, W. M.: Clinical and Pharmacologic Studies of Intramuscular Oxytetracycline, Antibiotics & Chemother. **4**:1037-1044 (Oct.) 1954.

104. Kagan, B. M.; Mendelsohn, R. S.; Miller, R. A., and Elegant, L. D.: Subcutaneous Administration of Oxytetracycline, Antibiotics & Chemotherap. **4**:308-312 (March) 1954.

105. Scott, R. L.; Colalongo, S. F., and Oldroyd, N. O., Jr.: Destruction Rates of Procaine Penicillin and Dibenzylethylenediamine Dipenicillin: An in Vitro Study, Antibiotics & Chemother. **4**:691-696 (June) 1954.

106. Walkenstein, S. S.; Chumakow, N., and Seifter, J.: Fate and Sojourn of Dibenzylethylenediamine C^{14}-Dipenicillin G and C^{14}-Penicillin G Following Oral and Intramuscular Injection, Antibiotics & Chemother. **4**:1245-1250 (Dec.) 1954.

107. Walkenstein, S. S.; Kuna, M., and Seifter, J.: Fate and Sojourn of C^{14}-Dibenzylethylenediamine (DBED) and C^{14}-DBED Dipenicillin G (Bicillin) Following Oral and Intramuscular Injection, Antibiotics & Chemother. **4**:700-706 (June) 1954.

108. Perry, C. B., and Gillespie, W. A.: Intramuscular Benzathene Penicillin in the Prophylaxis of Streptococcal Infection in Rheumatic Children, Brit. M. J. **2**:729-730 (Sept. 25) 1954.

109. Hankins, J. R., and Yeager, G. H.: Use of a New Long-Acting Penicillin Compound in Surgical Infections, J. A. M. A. **155**:1306-1307 (Aug. 7) 1954.

110. Diehl, A. M.; Hamilton, T. R.; Keeling, I. C., and May, J. S.: Long-Acting Repository Penicillin in Prophylaxis of Recurrent Rheumatic Fever, J. A. M. A. **155**:1466-1470 (Aug. 21) 1954.

111. Chamovitz, R.; Catanzaro, F. J.; Stetson, C. A., and Rammelkamp, C. H., Jr.: Prevention of Rheumatic Fever by Treatment of Previous Streptococcal Infections: I. Evaluation of Benzathine Penicillin G, New England J. Med. **251**:466-471 (Sept. 16) 1954.

112. Tunevall, G., and Hedenius, P.: Laboratory and Clinical Studies with Erythromycin, Antibiotics & Chemother. **4**:678-683 (June) 1954.

113. Selbie, F. R.: Comparison of Sodium and Procaine Penicillin in Treatment of Experimental Staphylococcal Infection in Mice, Brit. M. J. **1**:1350-1353 (June 12) 1954.

114. Hofer, J. W., and McCaskey, G. M.: Infections Occurring During Antimicrobial Therapy, A. M. A. Arch. Int. Med. **93**:44-52 (Jan.) 1954.

115. Weinstein, L.; Goldfield, M., and Chang, T. W.: Infections Occurring During Chemotherapy: A Study of Their Frequency, Type and Predisposing Factors, New England J. Med. **251**:247-255 (Aug. 12) 1954.

116. Robinson, H. M., Jr.: Moniliasis Complicating Antibiotic Therapy, A. M. A. Arch. Dermat. & Syph. **70**:640-652 (Nov.) 1954.

117. Still, W. J.: Sensitivity to Penicillin Causing an Acute Abdominal Emergency, Brit. M. J. **2**: 1032 (Oct. 30) 1954.

118. Fisher, S.: Fatality Following Penicillin Injection, Ann. Int. Med. **40**:1227-1230 (June) 1954.

119. Campbell, P. E.: Sudden Death in Labour Following an Injection of Penicillin, Brit. M. J. **1**:87-88 (Jan. 8) 1955.

120. Rosenthal, A.: Eight Fatal Anaphylactic Reactions to Penicillin, New York J. Med. **54**:1485-1487 (May 15) 1954.

121. Welch, H.; Lewis, C. N., and Kerlan, I.: Blood Dyscrasias: A Nationwide Survey, Antibiotics & Chemother. **4**:607-623 (June) 1954.

122. Pickard, K., and Rosenblatt, P.: Aplastic Anemia Due to Chloromycetin Toxicity, New York J. Med. **54**:1784-1790 (June 15) 1954.

123. Genkins, G.; Uhr, J. W., and Bryer, M. S.: Bacitracin Nephropathy: Report of a Case of Acute Renal Failure and Death, J. A. M. A. **155**:894-897 (July 3) 1954.

124. Katz, S.; Badger, G. F.; Jordan, W. S., Jr.; Rosenbaum, H. B., and Dingle, J. H.: A Study of Illness in a Group of Cleveland Families: VI. Controlled Study of Reactions to Oxytetracycline Hydrochloride, New England J. Med. **251**:508-513 (Sept. 23) 1954.

125. Milberg, M. B.; Kamhi, B., and Banowitch, M. M.: Pharmacology and Therapeutic Efficacy of Tetracycline, Antibiotics & Chemother. **4**:1086-1099 (Oct.) 1954.

126. Marr, W. G.; Wood, R., and Grieves, M.: Further Studies on the Effect of Agents on Regeneration of Corneal Epithelium, Am. J. Ophth. **37**:544-548 (April) 1954.

127. Welch, H.: The Manual of Antibiotics, New York, Medical Encyclopedia, Inc., 1954.

128. Perdrup, A.; Heilesen, B., and Sylvest, B.: Follow-Up Examination of 157 Patients with Early Mucocutaneous Syphilis Treated with Penicillin and Followed for One to Four Years, Acta dermat.-venereol. **34**:133-135, 1954.

129. vom Hofe, K., and Wustenberg, W.: Zur Frage der Penicillin-Prophylaxe bei perforierenden Verletzungen, Klin. Monatsbl. Augenh. **124**:534-536, 1954.

130. Gibson, C. D.; Nushan, H., and Anderson, D. N.: Treatment of Bacterial Pneumonia with Erythromycin: A Controlled Clinical Study, Ann. Int. Med. **41**:112-117 (July) 1954.

131. Blute, J. F., Jr.: Use of Erythromycin in Diphtheria, New England J. Med. **251**:70-71 (July 8) 1954.

132. Shoemaker, E. H., and Yow, E. M.: Clinical Evaluation of Erythromycin, A. M. A. Arch. Int. Med. **93**:397-406 (March) 1954.

133. Prater, B. G., and Moor, W. A.: Erythromycin: A Report on a New Ophthalmic Ointment, Am. J. Ophth. **37**:938-939 (June) 1954.

134. Agarwal, L. P., and Saxena, R. P.: Erythromycin in Trachoma, Brit. J. Ophth. **38**:690-691 (Nov.) 1954.

135. Button, R. R.: Treatment of Trachoma with Erythromycin: A Preliminary Report of 21 Cases, Am. J. Ophth. **39**:223-227 (Feb.) 1955.

136. Sanford, J. P.; Favour, C. B.; Harrison, J. H., and Mao, F. H.: Tetracycline in Genitourinary Infections, New England J. Med. **251**:810-813 (Nov. 11) 1954.

137. Glatt, M., and Ross, S.: Tetracycline in the Treatment of Bacterial Pneumonia in Children: A Preliminary Report, Antibiotics & Chemother. **4**: 395-401 (April) 1954.

138. English, A. R.; P'An, S. Y.; McBride, T. J.; Gardocki, J. F.; Van Halsema, G., and Wright, W. A.: Tetracycline—Microbiologic, Pharmacologic, and Clinical Evaluation, Antibiotics & Chemother. **4**:411-422 (April) 1954.

139. Palazzolo, A. J.; Eisenberg, G. M.; Foltz, E. L.; Sones, M., and Flippin, H. F.: Tetracycline Therapy of Pneumococcal Pneumonia, Antibiotics & Chemother. **4**:1075-1081 (Oct.) 1954.

140. Marmell, M., and Prigot, A.: Tetracycline in the Treatment of Certain Venereal Diseases, Antibiotics & Chemother. **4**:1117-1121 (Oct.) 1954.

141. Welch, H.; Randall, W. A.; Reedy, R. J., and Oswald, E. J.: Variations in Antimicrobial Activity of the Tetracyclines, Antibiotics & Chemother. **4**:741-745 (July) 1954.

142. English, A. R.; McBride, T. J.; Simon, D. L., and Mullady, H. E.: Additional Studies on the Chemotherapeutic Efficacy of Tetracycline, Antibiotics & Chemother. **4**:1082-1085 (Oct.) 1954.

143. Korff, J.: Biophtal: Ein neues Kombinationsantibioticum in der Augenheilkunde, Ophthalmologica **127**:418-422 (June) 1954.

144. Lipsius, E. L.: Postoperative Endophthalmitis, Am. J. Ophth. **37**:897-903 (June) 1954.

145. Menon, P. G.; Raskin, H. F., and Woodward, T. E.: Further Experience with Chloramphenicol in the Treatment of Meningococcal Meningitis, Antibiotics & Chemother. **4**:1113-1116 (Oct.) 1954.

146. Lopez, S. P.: Topical Use of Neomycin in Ophthalmology: A Preliminary Report, Antibiotics & Chemother. **4**:1189-1195 (Dec.) 1954.

147. Church, R.: Neomycin in Pyogenic Skin Diseases, Brit. M. J. **1**:314-315 (Feb. 6) 1954.

148. Williams, R. K.; Hench, M. E., and Guerry, DuP., III: Pyocyaneus Ulcer: Clinical Report and Experimental Investigation, Am. J. Ophth. **37:** 538-544 (April) 1954.

149. Biehl, J. P., and Hamburger, M.: Polymyxin B Therapy of Meningitis Following Procedures on Central Nervous System, A. M. A. Arch. Int. Med. **93:**367-378 (March) 1954.

150. Agarwal, L. P., and Gupta, B. M.: Sulphonamides and Antibiotic Drugs in the Treatment of Trachoma, Brit. J. Ophth. **38:**119-122 (Feb.) 1954.

151. Pavković-Bugarski, G.: Le Role de l'aureomycine et de la terramycine dans la thérapie du trachome, Ophthalmologica **128:**180-196 (Sept.) 1954.

152. Pavković-Bugarski, G., and Cvetojević, M.: Terramycin in Trachoma, Brit. J. Ophth. **38:**692-698 (Nov.) 1954.

153. Lazarus, A. S., and Farpour, M.: Relative Frequency and Mass Treatment of Trachoma in Southern Iran, Am. J. Ophth. **38:**665-672 (Nov.) 1954.

154. Laing, C. R., and Scott, R. B.: Erythromycin-Polymyxin Ointment in the Treatment of Pyoderma in Children, Antibiotics & Chemother. **4:**641-646 (June) 1954.

155. Pass, B. J., and Rattner, H.: Treatment of Pyoderma with Polymyxin B-Bacitracin Ointment, J. A. M. A. **155:**1153 (July 24) 1954.

156. Philip, A. J.: Bacitracin-Polymyxin B Sulfate Lotion, Antibiotics & Chemother. **4:**763-774 (July) 1954.

157. Barr, F. S.; Carman, P. E., and Harris, J. R.: Synergism and Antagonism in Antibiotic Combinations, Antibiotics & Chemother. **4:**818-821 (July) 1954.

158. Manten, A.: Synergism and Antagonism Between Antibiotic Mixtures Containing Erythromycin, Antibiotics & Chemother. **4:**1228-1233 (Dec.) 1954.

159. d'Ermo, F., and di Giulio, F.: Sull'Azione in vitro di talune associazioni di antibiotici sui germi patogen oculari, Boll. ocul. **33:**80-99 (Feb.) 1954.

160. Jawetz, E.; Coleman, V., and Gunnison, J. B.: Participation of Polymyxin B in Combined Antibiotic Action, Ann. Int. Med. **41:**79-88 (July) 1954.

161. Benigno, P.; Berti, T., and Cima, L.: Action of Erythromycin Alone and Associated with Oxytetracycline and Penicillin on Staphylococcus Aureus, Antibiotics & Chemother. **4:**1143-1151 (Nov.) 1954.

162. Hart, J. J. D.; Piepes, S. L.; Anderson, F. E.; Barkley, F. A., and Mast, G. W.: p-Aminosalicylic Acid Hydrazide in Vitro Activity Against Mycobacterium Tuberculosis, Antibiotics & Chemother. **4:**809-812 (July) 1954.

163. Steenken, W., Jr.; Wolinsky, E., and Montalbine, V.: Effect of 2 Isoniazid Derivatives and PAS Hydrazide on Isoniazid Susceptible and Resistant Tubercle Bacille, Proc. Soc. Exper. Biol. & Med. **87:**245-250 (Oct.) 1954.

164. Streptomycin-Resistant Tubercle Bacilli As a Public-Health Hazard, Editorial, New England J. Med. **251:**584-585 (Sept. 30) 1954.

165. Appelbaum, E., and Anderson, T. A.: Treatment of Tuberculous Meningitis with Isonicotinic Acid Hydrazides, J. A. M. A. **156:**673-676 (Oct. 16) 1954.

166. Blumenthal, B.: Some Cases of Lupus Vulgaris Treated with Isonicotinic Acid Hydrazide (INH), Acta dermat.-venereol. **34:**11-16, 1954.

167. Wehnert, R. A.: Lupus Vulgaris Treated with INH: A Preliminary Report, Acta dermat.-venereol. **34:**173-179, 1954.

168. Kendig, E. L. Jr.; Trevathan, G. E., and Ownby, R., Jr.: Isoniazid in Treatment of Tuberculosis in Childhood, A. M. A. Am. J. Dis. Child. **88:**148-157 (Aug.) 1954.

169. Lawson, J. H.; Lees, A. W.; Allan, G. W., and McKenzie, P.: Streptomycin and Isoniazid in Acute Miliary Tuberculosis, Brit. M. J. **2:**840-842 (Oct. 9) 1954.

170. Pasieczny, T.: Streptomycin and Isoniazid in Treatment of Erythema Induratum (Bazin's Disease), A. M. A. Arch. Dermat. & Syph. **70:**514-515 (Oct.) 1954.

171. Ogilvie, C. M.: Bacterial Resistance to Isoniazid and "Marsilid" in Treatment of Pulmonary Tuberculosis: Results of Trials, Brit. M. J. **2:**829-833 (Oct. 9) 1954.

172. Stewart, S. M.; Turnbull, F. W., and Crofton, J. W.: Use of Oxytetracycline in Preventing or Delaying Isoniazid Resistance in Pulmonary Tuberculosis, Brit. M. J. **2:**1508-1511 (Dec. 25) 1954.

173. Knapp, P., and von Sallmann, L.: Treatment of Experimental Ocular Tuberculosis with Isoniazid, Am. J. Ophth. **38:**199-205 (July, Pt. II) 1954.

174. Simonelli, M., and Rizzini, V.: L'Idrazide dell'acido isonicotinico in oftalmologia: IV. Risultati terapeutici ottenuti in 60 casi di affezioni tubercolar dell'occhio, Gior. ital. oftal. **7:**199-202 (May-June) 1954.

175. Eadie, S.: Primary Tuberculosis of the Conjunctiva Treated with Streptomycin and PAS, Brit. J. Ophth. **38:**568-570 (Sept.) 1954.

176. Woods, A. C.: Pathogenesis and Treatment of Ocular Tuberculosis, A. M. A. Arch. Ophth. **52:**174-196 (Aug.) 1954.

177. Korst, D. R.: Severe Reactions to Para-Aminosalicylic Acid: A Case Report and Brief Review of Literature, Ann. Int. Med. **40:**1011-1016 (May) 1954.

178. Balint, J. A.; Fraser, R., and Hanno, M. G.: Radio-Iodine Measurements of Thyroid Function During and After PAS Treatment of Tuberculosis, Brit. M. J. **1**:1234-1237 (May 29) 1954.

179. Bloch, R. G.; Dooneief, A. S.; Buchberg, A. S., and Spellman, S.: Clinical Effect of Isoniazid and Iproniazid in the Treatment of Pulmonary Tuberculosis, Ann. Int. Med. **40**:881-900 (May) 1954.

180. Pleasure, H.: Psychiatric and Neurological Side-Effects of Isoniazid and Iproniazid, A. M. A. Arch. Neurol. & Psychiat. **72**:313-320 (Sept.) 1954.

181. Wiedorn, W. S., and Ervin, F.: Schizophrenic-like Psychotic Reactions with Administration of Isoniazid, A. M. A. Arch. Neurol. & Psychiat. **72**:321-324 (Sept.) 1954.

182. Rosen, F.: Effect of Isonicotinic Acid Hydrazide on Niacin and Pyridoxine Metabolism in Rats, Proc. Soc. Exper. Biol. & Med. **88**:243-246 (Feb.) 1955.

183. Biehl, J. P., and Vilter, R. W.: Effects of Isoniazid on Pyridoxine Metabolism, J. A. M. A. **156**:1549-1552 (Dec. 25) 1954.

184. Mudie, I. S.; Horne, N. W., and Crofton, J. W.: Isoniazid and Weight Gain, Brit. M. J. **1**:1304-1305 (June 5) 1954.

185. Rebhun, J.; Feinberg, S. M., and Zeller, E. A.: Potentiating Effect of Iproniazid on Action of Some Sympathicomimetic Amines, Proc. Soc. Exper. Biol. & Med. **87**:218-220 (Oct.) 1954.

186. Summers, W. A.: Chemotherapeutic Efficacy of 2,4-Diamino-5-p-Chlorophenyl-6-Ethylpyrimidine (Daraprim) in Experimental Toxoplasmosis, Am. J. Trop. Med. **2**:1037-1044, 1953.

187. Isaacs, R.: Treatment of Polycythemia Vera with Daraprim, J. A. M. A. **156**:1491-1493 (Dec. 18) 1954.

188. Giblin, W. E.: "Daraprim" in the Whagi Valley of New Guinea, M. J. Australia **1**:9-10 (Jan. 2) 1954.

189. Gunther, C. E.: A Fatal Overdose of "Daraprim," M. J. Australia **2**:970 (Dec. 18) 1954.

190. Beverley, J. K.; Beattie, C. P., and Fry, B. A.: Experimental Toxoplasmosis of the Uveal Tract, Brit. J. Ophth. **38**:489-496 (Aug.) 1954.

191. Dubois, E. L.: Quinacrine (Atabrine) in Treatment of Systemic and Discoid Lupus Erythematosus, A. M. A. Arch. Int. Med. **94**:131-141 (July) 1954.

192. Helanen, S.: Treatment of Chronic Discoid Lupus Erythematosus with Atabrine, Acta dermat.-venereol. **34**:59-66, 1954.

193. Woodburne, A. R.; Philpott, O. S., and Philpott, J. A., Jr.: Quinacrine (Atabrine) in Treatment of Solar Dermatoses, A. M. A. Arch. Dermat. & Syph. **70**:116-118 (July) 1954.

194. Bereston, E. S.: Use of Selenium Sulfide Shampoo in Seborrheic Dermatitis, J. A. M. A. **156**:1246-1247 (Nov. 27) 1954.

195. Cohen, L. B.: Use of Selsun in Blepharitis Marginalis, Am. J. Ophth. **38**:560-562 (Oct.) 1954.

196. Gunn, J. A., and Cooke, A. M.: Pilocarpine As an Antagonist to the Undesired Effects of Ganglion-Blocking Agents in the Treatment of Hypertension, Brit. M. J. **1**:1473 (June 26) 1954.

197. Okinaka, A. J.; Doull, J.; Cocn, J. M., and DuBois, K. P.: Studies on the Toxicity and Pharmacological Actions of *Bis* (Dimethylamido) Fluorophosphate (BFP), J. Pharmacol. & Exper. Therap. **112**:231-245 (Oct.) 1954.

198. Gerewitz, H.: Über Zystenbildung am Pupillarpigmentsaum mit Mioticis behandelter Glaukomaugen, Klin. Monatsbl. Augenh. **124**:521-528, 1954.

199. Hallermann, W.: Beitrag zur Operationsindikation des primären Glaukoms, Klin. Monatsbl. Augenh. **124**:513-516, 1954.

200. Swan, K. C.: Iris Pigment Nodules Complicating Miotic Therapy, Am. J. Ophth. **37**:886-889 (June) 1954.

201. Westsmith, R. A., and Abernethy, R. E.: Detachment of Retina with Use of Diisopropyl Fluorophosphate (Flurophryl) in Treatment of Glaucoma, A. M. A. Arch. Ophth. **52**:779-780 (Nov.) 1954.

202. Diamant, H.: Cataract Due to Cholinesterase Inhibitors in the Guinea-Pig, Acta ophth. **32**:357-361 (April) 1954.

203. Austin, L., and Davies, D. R.: The Part Played by Inhibition of Cholinesterases of the CNS in Producing Paralysis in Chickens, Brit. J. Pharmacol. **9**:145-152 (June) 1954.

204. Barnes, J. M., and Duff, J. I.: Acetylcholine Production in Animals Poisoned by Diethyl-*p*-Nitrophenyl Phosphate (Paraoxon), Brit. J. Pharmacol. **9**:153-158 (June) 1954.

205. Niedermeier, W.; Stone, R. E.; Dreizen, S., and Spies, T. D.: Effect of 2-Acetylamino-1,3,4-Thiadiazole-5-Sulfonamide (Diamox) on Sodium, Potassium, Bicarbonate and Buffer Content of Saliva, Proc. Soc. Exper. Biol. & Med. **88**:273-275 (Feb.) 1955.

206. Kleeman, C. R.; Bass, D. E., and Quinn, M.: Effect of 6063, Sodium Bicarbonate and Ammonium Chloride on Electrolyte Composition of Thermal Sweat, Proc. Soc. Exper. Biol. & Med. **88**:253-256 (Feb.) 1955.

207. Leaf, A.; Schwartz, W. B., and Relman, A. S.: Oral Administration of a Potent Carbonic Anhydrase Inhibitor (Diamox): I. Changes in Electrolyte and Acid-Base Balance, New England J. Med. **250**:759-764 (May 6) 1954.

208. Heiskell, C. L., Jr.; Belsky, J. B., and Klaumann, B. F.: Treatment of Chronic Emphysema of Lungs with Diamox (Carbonic Anhydrase Inhibitor), J. A. M. A. **156**:1059-1063 (Nov. 13) 1954.

209. Breinin, G. M., and Görtz, H.: Carbonic Anhydrase Inhibitor Acetazoleamide (Diamox): A New Approach to the Therapy of Glaucoma, A. M. A. Arch. Ophth. **52**:333-348 (Sept.) 1954.

210. Grant, W. M., and Trotter, R. R.: Diamox (Acetazoleamide) in Treatment of Glaucoma, A. M. A. Arch. Ophth. **51**:735-739 (June) 1954.

211. Malbran, J. L.; San Martin, F. J.; Cabanne, G. R., and Paunessa, J.: Diamox y tension ocular, Arch. oftal. Buenos Aires **29**:576-583 (Nov.) 1954.

212. Green, H.; Capper, S. A.; Bocher, C. A., and Leopold, I. H.: Effect of Acetazoleamide (Diamox) on Carbonic Anhydrase Activity of Anterior Uvea of the Rabbit Eye, A. M. A. Arch. Ophth. **52**:758-762 (Nov.) 1954.

213. Becker, B.: Mechanism of the Fall in Intraocular Pressure Induced by the Carbonic Anhydrase Inhibitor, Diamox, Am. J. Ophth. **39**: 177-184 (Feb., Pt. II) 1955.

214. Tschirgi, R. D.; Frost, R. W., and Taylor, J. L.: Inhibition of Cerebrospinal Fluid Formation by a Carbonic Anhydrase Inhibitor, 2-Acetylamino-1,3,4-Thiadiazole-5-Sulfonamide (Diamox), Proc. Soc. Exper. Biol. & Med. **87**:373-376 (Nov.) 1954.

215. Pearson, J. R.; Binder, C. I., and Neber, J.: Agranulocytosis Following Diamox Therapy, J. A. M. A. **157**:339-341 (Jan. 22) 1955.

216. Schwimmer, J.; Schaffer, A. I., and Guido, J.: Febrile Reaction to Acetazoleamide (Diamox), New York J. Med. **54**:692-693 (March 1) 1954.

217. Leydhecker, W.: Die Wirkung von Homatropin auf die Tension des gesunden und des glaukomkranken Auges, von Graefes Arch. Ophth. **155**:386-396 (June) 1954.

218. Gordon, D. M., and Ehrenberg, M. H.: Cyclopentolate Hydrochloride: A New Mydriatic and Cycloplegic Agent, Am. J. Ophth. **38**:831-838 (Dec.) 1954.

219. Abrahamson, I. A., Jr., and Hurwitz, P.: Oxyphenonium (Antrenyl), a Substitute for Atropine: A Clinical Study, A. M. A. Arch. Ophth. **52**:519-523 (Oct.) 1954.

220. Havener, W. H., and Falls, H. F.: Oxyphenonium (Antrenyl): A Potent Atropine Substitute, A. M. A. Arch. Ophth. **52**:515-518 (Oct.) 1954.

221. Hery, J., and Le Dourneuf, G.: Un Cas d'intoxication par le collyre à l'atropine, Bull. Soc. opht. France, pp. 158-160, January, 1954.

222. von Euler, U. S.: Physiologic Basis for the Clinical Use of Noradrenalin, Ann. Int. Med. **41**: 699-708 (Oct.) 1954.

223. Ahlquist, R. P.; Taylor, J. P.; Rawson, C. W., Jr., and Sydow, V. L.: Comparative Effects of Epinephrine and Levarterenol in the Intact Anesthetized Dog, J. Pharmacol. & Exper. Therap. **110**:352-360 (March) 1954.

224. Hall, B.: Recovery of Patient in Prolonged Shock After Arterenol Therapy, J. A. M. A. **157**: 653-654 (Feb. 19) 1955.

225. Page, I. H.: Serotonin (5-Hydroxytryptamine), Physiol. Rev. **34**:563-588 (July) 1954.

226. Walter, W. G.; van Gemert, A. G., and Duyff, J. W.: Kinetics of Pupillary Dilation Induced by Administration of L-Epinephrine, Acta physiol. et pharmacol. neerl. **3**:309-324 (Oct.) 1954.

227. Hofmann, H.: Nor-Adrenalin in der Augenheilkunde, Klin. Monatsbl. Augenh. **124**:63-76, 1954.

228. Weekers, R.; Prijot, E., and Gustin, J.: Mésure de la résistance à l'écoulement de l'humeur aqueuse au moyen du tonomètre électronique: VI. Mode d'action de l'adrénaline dans le glaucome chronique, Ophthalmologica **128**:213-217 (Oct.) 1954.

229. Teitgen, R. E.: Single Instillation of Cycloplegic Solutions, Am. J. Ophth. **37**:940-941 (June) 1954.

230. Fellows, E. J.; McLean, R. A.; Macko, E.; Kerwin, J. F.; Hall, G. C.; Milnes, F. J.; Witt, I. H., and Ullyot, G. E.: Oral and Intravenous Adrenolytic Activity of a Number of N-benzyl-N-Phenoxyethyl and N-Benzyl-N-Phenoxyisopropyl-β-Chlorethylamines, J. Pharmacol. & Exper. Therap. **110**:463-469 (April) 1954.

231. Harris, J. E.; Gehrsitz, L. B., and Heinrichs, D.: Effect of Dibenamine and Certain of Its Congeners on Aqueous Humor Dynamics, Transactions of the 17th International Congress of Ophthalmology, to be published.

232. Agarwal, L. P.: Treatment of Glaucoma with Hydergine, Ophthalmologica **127**:25-33 (Jan.) 1954.

233. Caselli, F.: La Permeabilità della barriera emato-oftalmica sotto l'azione della diidroergotamina, Boll. ocul. **33**:745-753 (Nov.) 1954.

234. Leydhecker, W.: Die Priscolprobe bei Glaukom, Klin. Monatsbl. Augenh. **125**:57-61, 1954.

235. Henkes, H. E.: Electroretinogram in Circulatory Disturbances of the Retina: IV. Electroretinogram in Cases of Retinal and Choroidal Hypertension and Arteriosclerosis, A. M. A. Arch. Ophth. **52**:30-41 (July, Pt. I) 1954.

236. Jacobson, J. H., and Lincoln, M. W.: Effect of Vasodilator Drugs and Stellate Ganglion Block upon the Electroretinogrm. A. M. A. Arch. Ophth. **52**:917-922 (Dec.) 1954.

237. Zahn, K., and Šimcová, M.: Die Wirkung von Priscol auf die Blutzirkulation der Netzhaut: IV. Experimentell-pharmakologische Studie, Ophthalmologica **129**:44-52 (Jan.) 1955.

238. Šimcová, M., and Zahn, K.: Ein Behandlungsversuch der hypertonischen Retinopathie mit Hydergin, Ophthalmologica **128**:218-231 (Oct.) 1954.

239. Remler, O.: Hyderginanwendung bei Durchblutungsstörungen der Netzhaut, Klin. Monatsbl. Augenh. **124**:713-734, 1954.

240. Herbst, W.: Beobachtungen über das Verhalten hypertonischer Augenhintergrundveränderungen unter dem Einfluss von Hydergin, Klin. Monatsbl. Augenh. **124**:446-457, 1954.

241. Duff, F.; Patterson, G. C., and Shepherd, J. T.: A Quantitative Study of the Response to Adenosine Triphosphate of the Blood Vessels of the Human Hand and Forearm, J. Physiol. **125**: 581-589 (Sept.) 1954.

242. Holton, F. A., and Holton, P.: The Capillary Dilator Substances in Dry Powders of Spinal Roots: A Possible Role of Adenosine Triphosphate in Chemical Transmission from Nerve Endings, J. Physiol. **126**:124-140 (Oct.) 1954.

243. Perry, W. L., and Reinert, H.: Effects of Preganglionic Denervation on the Reactions of Ganglion Cells, J. Physiol. **126**:101-115 (Oct.) 1954.

244. Rapisarda, D.: Azione di un farmaco ganglioplegico ("Pendiomid") sull'occhio, Boll. ocul. **33**:321-346 (June) 1954.

245. Smirk, F. H.: Results of Methonium Treatment of Hypertensive Patients, Brit. M. J. **1**:717-723 (March 27) 1954.

246. Strazzi, A.: I Composti di metonio nella terapia delle affezioni vascolari della retina, Boll. ocul. **33**:385-399 (July) 1954.

247. Cronheim, G.; Brown, W.; Cawthorne, J., Tockes, M. I. and Ungari J.: Pharmacological Studies with Rescinnamine; A New Alkaloid Isolated from Rauwolfia Serpentina, Proc. Soc. Exper. Biol. & Med. **86**:120-124 (May) 1954.

248. Slater, I. H.; Rathbun, R. C.; Henderson, F. G., and Neuss, N.: Pharmacological Properties of Recanescine, a New Sedative Alkaloid from Rauwolfia Canescens Linn, Proc. Soc. Exper. Biol. & Med. **88**:293-295 (Feb.) 1955.

249. Goth, A., and Harrison, F.: Influence of Protoveratrine on Effect of Vasoactive Drugs, Proc. Soc. Exper. Biol. & Med. **87**:437-439 (Nov.) 1954.

250. Chen, G.; Ensor, C. R., and Bohner, B.: A Facilitation Action of Reserpine on the Central Nervous System, Proc. Soc. Exper. Biol. & Med. **86**:507-510 (July) 1954.

251. Chen, G., and Ensor, C. R.: Antagonism Studies on Reserpine and Certain CNS Depressants, Proc. Soc. Exper. Biol. & Med. **87**:602-608 (Dec.) 1954.

252. Rein, C. R., and Goodman, J. J.: Efficacy of Reserpine (Serpasil) in Dermatological Therapy, A. M. A. Arch. Dermat. & Syph. **70**:713-717 (Dec.) 1954.

253. Noce, R. H.; Williams, D. B., and Rapaport, W.: Reserpine (Serpasil) in the Management of the Mentally Ill and Mentally Retarded: A Preliminary Report, J. A. M. A. **156**:821-824 (Oct. 30) 1954.

254. Perera, G. A.: Rauwolfia Serpentina in Hypertensive Vascular Disease, Proc. Soc. Exper. Biol. & Med. **86**:453-456 (July) 1954.

255. Wilkins, R. W.; Judson, W. E.; Stone, R. W.; Hollander, W.; Huckabee, W. E., and Friedman, I. H.: Reserpine in the Treatment of Hypertension, New England J. Med. **250**:477-478 (March 18) 1954.

256. Taylor, R. D.; Corcoran, A. C.; Dustan, H. P., and Page, I. H.: Further Evaluation of Hydralazine in Treatment of Hypertensive Disease, A. M. A. Arch. Int. Med. **93**:705-712 (May) 1954.

257. Livesay, W. R.; Moyer, J. H., and Miller, S. I.: Treatment of Hypertension with Rauwolfia Serpentina Alone and Combined with Other Drugs: Results in 84 Cases, J. A. M. A. **155**:1027-1035 (July 17) 1954.

258. Hoobler, S. W.: Treatment of Hypertension, Am. J. Med. **17**:259-270 (Aug.) 1954.

259. Corcoran, A. C.; Dustan, H. P.; Taylor, R. D., and Page, I. H.: Management of Hypertensive Disease, Am. J. Med. **17**:383-394 (Sept.) 1954.

260. Schroeder, H. A.: Management of Arterial Hypertension, Am. J. Med. **17**:540-561 (Oct.) 1954.

261. Thiel, R.: Die medikamentose Therapie des primären Glaukoms, Klin. Monatsbl. Augenh. **125**: 513-530, 1954.

262. Freis, E. D.: Mental Depression in Hypertensive Patients Treated for Long Periods with Large Doses of Reserpine, New England J. Med. **251**:1006-1008 (Dec. 16) 1954.

263. Feder, I. A.: Febrile Syndrome During Prolonged Hydralazine Treatment for Hypertension, New England J. Med. **251**:273-274 (Aug. 12) 1954.

264. Reinhardt, D. J., and Waldron, J. M.: Lupus Erythematosus-like Syndrome Complicating Hydralazine (Apresoline) Therapy, J. A. M. A. **155:** 1491-1492 (Aug. 21) 1954.

265. Shackman, N. H.: Swiller, A. I., and Morrison, M.: Syndrome Simulating Acute Disseminated Lupus Erythematosus: Appearance After Hydralazine (Apresoline) Therapy, J. A. M. A. **155:**1492-1494 (Aug. 21) 1954.

266. Thesleff, S., and Unna, K. R.: Differences in Mode of Neuromuscular Blockade in a Series of Symmetric Bis-Quaternary Ammonium Salts, J. Pharmacol. & Exper. Therap. **111:**99-113 (May) 1954.

267. Papst, W.: Succinyl-bis-Cholinester als Muskelrelaxans und Hyaluronidase bei der Staroperation, Klin. Monatsbl. Augenh. **124:**536-545, 1954.

268. Jayle, G. E.; Jaquenoud, P., and Haudiquet, M.: La Curarisation à l'état de veille en chirurgie oculaire, Ophthalmologica **127:**129-131 (March) 1954.

269. Mather, R. W.; Shuman, C. R., and Harrison, S. I.: Influences of Curare and Eserine on Ocular Tension Following Electroshock, Am. J. Ophth. **37:**859-866 (June) 1954.

270. Manning, E. L., and Hollander, W. M.: Glaucoma and Electroshock Therapy, Am. J. Ophth. **37:**857-859 (June) 1954.

271. Dresel, P. E.; Underwood, E. E., and Richarson, A. P.: Correlation of Plasma Level with Spinal Cord Depressant Action of Mephenesin and Its Carbamic Acid Ester, Proc. Soc. Exper. Biol. & Med. **86:**621-623 (July) 1954.

272. King, E. E., and Unna, K. R.: Action of Mephenesin and Other Interneuron Depressants on the Brain Stem, J. Pharmacol. & Exper. Therap. **111:***293*-301 (July) 1954.

273. Diaz-Rivera, R. S.; Trilla, F., and Pons, E. R., Jr.: Muscular Relaxation in Tetanus with Special Reference to the Effect of Mephenesin, Ann. Int. Med. **40:**563-580 (March) 1954.

274. Parkes, C. M.: Mephenesin and Gallamine Triethiodide in Tetanus, Brit. M. J. **2:**445-446 (Aug. 21) 1954.

275. Lasagna, L.: Nalorphine (N-Allylnormorphine): Practical and Theoretical Considerations, A. M. A. Arch. Int. Med. **94:**532-558 (Oct.) 1954.

276. Green, A. F.; Ruffell, G. K., and Walton, E.: Morphine Derivatives with Antianalgesic Action, J. Pharm. & Pharmacol. **6:**390-397 (June) 1954.

277. Gruber, C. M., Jr.: Effect of Levallorphan Tartrate upon Toxicity of Morphine, Proc. Soc. Exper. Biol. & Med. **88:**189-191 (Feb.) 1955.

278. Winter, C. A.; Orahovats, P. D.; Flataker, L.; Lehman, E. G., and Lehman, J. T.: Studies on the Pharmacology of N-Allylnormorphine, J. Pharmacol. & Exper. Therap. **111:**152-160 (June) 1954.

279. Salomon, A.; Marcus, P. S.; Herschfus, J. A., and Segal, M. S.: N-Allylnormorphine (Nalline) Action on Narcotized and Non-Narcotized Subjects, Am. J. Med. **17:**214-222 (Aug.) 1954.

280. Winter, C. A.; Gaffney, C. E., and Flataker, L.: Effect of N-Allylnormorphine upon the Antidiuretic Action of Morphine, J. Pharmacol. & Exper. Therap. **111:**360-364 (July) 1954.

281. Orahovats, P. D.; Winter, C. A., and Lehman, E. G.: Pharmacological Studies of Mixtures of Narcotics and N-Allylnormorphine, J. Pharmacol. & Exper. Therap. **112:**246-251 (Oct.) 1954.

282. Gruber, C. M., Jr.: Effect of N-Allylnormorphine upon the Toxicity of Morphine, J. Pharmacol. & Exper. Therap. **111:**404-408 (Aug.) 1954.

283. Gruber, C. M., Jr.: Effect of N-Allylnormorphine in the Presence of Secobarbital, J. Pharmacol. & Exper. Therap. **111:**409-412 (Aug.) 1954.

284. Vivante, A.; Kao, F. F., and Belford, J.: Effect of Nalorphine on the Respiration of Dogs Anesthetized with Pentobarbital Sodium, J. Pharmacol. & Exper. Therap. **111:**436-446 (Aug.) 1954.

285. Lasagna, L., and Beecher, H. K.: Optimal Dose of Morphine, J. A. M. A. **156:**230-234 (Sept. 18) 1954.

286. Rasor, R., and Crecraft, H. J.: Addiction to Meperidine (Demerol) Hydrochloride, J. A. M. A. **157:**654-657 (Feb. 19) 1955.

287. Illingworth, R. S.; Burke, J.; Doxiadis, S. A.; Lorber, J.; Philpott, M. G., and Stone, D. G.: Salicylates in Rheumatic Fever: An Attempt to Assess Their Value, Quart. J. Med. **23:** 177-213 (April) 1954.

288. Cronheim, G., and Hyder, N.: Effect of Salicylic Acid on Adrenal-Pituitary System: III. Studies on Mechanism of This Effect, Proc. Soc. Exper. Biol. & Med. **86:**409-413 (July) 1954.

289. Cochran, J. B.: Further Observations on the Metabolic Stimulating Effect of Salicylate, Brit. M. J. **1:**733-734 (March 27) 1954.

290. Sproull, D. H.: A Peripheral Action of Sodium Salicylate, Brit. J. Pharmacol. **9:**262-264 (Sept.) 1954.

291. Sproull, D. H.: The Glycogenolytic Action of Sodium Salicylate, Brit. J. Pharmacol. **9:**121-124 (March) 1954.

292. Bianchi, C.: Further Studies on Compounds Reducing Synovial Membrane Permeability, Brit. J. Pharmacol. **9**:166-169 (June) 1954.

293. Brodie, B. B.; Yü, T. F.; Burns, J. J.; Chenkin, T.; Paton, B. C.; Steele, J. M., and Gutman, A. B.: Observations on G-25671, a Phenylbutazone Analogue (4-(Phenylthioethyl)-1,2-Diphenyl-3,5-Pyrazolidinedione), Proc. Soc. Exper. Biol. & Med. **86**:884-887 (Aug.-Sept.) 1954.

294. Pemberton, M.: Use of Phenylbutazone in Rheumatoid Arthritis, Brit. M. J. **1**:490-493 (Feb. 27) 1954.

295. Toone, E. C., Jr., and Irby, W. R.: Evaluation of Phenylbutazone (Butazolidin) in the Treatment of Rheumatoid Spondylitis: Report of 50 Cases, Ann. Int. Med. **41**:70-78 (July) 1954.

296. Brodie, B. B.; Lowman, E. W.; Burns, J. J.; Lee, P. R.; Chenkin, T.; Goldman, A.; Weiner, M., and Steele, J. M.: Observations on the Antirheumatic and Physiologic Effects of Phenylbutazone (Butazolidin) and Some Comparisons with Cortisone, Am. J. Med. **16**:181-190 (Feb.) 1954.

297. Kuzell, W. C.; Schaffarzick, R. W.; Naugler, W. E.; Gaudin, G.; Mankle, E. A., and Brown, B.: Phenylbutazone (Butazolidin) in Gout, Am. J. Med. **16**::212-217 (Feb.) 1954.

298. Johnson, H. P., Jr.; Engleman, E. P.; Forsham, P. H.; Krupp, M. A.; Green, T. W., and Goldfien, A.: Effects of Phenylbutazone in Gout, New England J. Med. **250**:665-670 (April 22) 1954.

299. Bishop, C.; Beyer, A., and Talbott, J. H.: Isotopic Uric Acid in Gouty and Rheumatoid Arthritis Patients Treated with Probenecid and Phenylbutazone, Proc. Soc. Exper. Biol. & Med. **86**:760-762 (Aug.-Sept.) 1954.

300. Mason, R. M.: Effect of Phenylbutazone on Uric Acid Metabolism, Brit. M. J. **1**:788-792 (April 3) 1954.

301. Yourish, N.; Paton, B.; Brodie, B. B., and Burns, J. J.: Effect of Phenylbutazone (Butazolidin) on Experimentally Induced Ocular Inflammation, A. M. A. Arch. Ophth. **53**:264-266 (Feb.) 1955.

302. Autor, H.: Über Erfahrungen mit Irgapyrin in der Augenheilkunde, Klin. Monatsbl. Augenh. **125**:745-747, 1954.

303. Christensen, E.: Peptic Ulcer Perforation After Phenylbutazone Therapy, Brit. M. J. **2**:916-917 (Oct. 16) 1954.

304. Steel, S. J., and Moffatt, J. L.: Stevens-Johnson Syndrome and Granulocytopenia After Phenylbutazone, Brit. M. J. **1**:795 (April 3) 1954.

305. Wood, I. H.: Fatal Agranulocytosis Following Phenylbutazone, Brit. M. J. **1**:802 (April 3) 1954.

306. O'Brien, D. J., and Storey, G.: Death from Hypersensitivity Due to Phenylbutazone, Brit. M. J. **1**:792-794 (April 3) 1954.

307. Nassim, J. R., and Pilkington, T.: Multiple Visceral Lesions Due to Phenylbutazone Toxicity, Brit. M. J. **2**:1028-1029 (Oct. 30) 1954.

308. Lipsett, M. B., and Goldman, R.: Phenylbutazone Toxicity: Report of a Case of Acute Renal Failure, Ann. Int. Med. **41**:1075-1079 (Nov.) 1954.

309. Exley, K. A.: Depression of Autonomic Ganglia by Barbiturates, Brit. J. Pharmacol. **9**:170-181 (June) 1954.

310. Raventós, J.: Distribution in the Body and Metabolic Fate of Barbiturates, J. Pharm. & Pharmacol. **6**:217-235 (April) 1954.

311. Butler, T. C.; Mahafee, C., and Waddell, W. J.: Phenobarbital: Studies of Elimination, Accumulation, Tolerance, and Dosage Schedules, J. Pharmacol. & Exper. Therap. **111**:425-435 (Aug.) 1954.

312. Fraser, H. F.; Isbell, H.; Eisenman, A. J.; Wikler, A., and Pescor, F. T.: Chronic Barbiturate Intoxication, A. M. A. Arch. Int. Med. **94**:34-41 (July) 1954.

313. Wasmuth, C. E., and Hale, D. E.: Thiopental Sodium Anesthesia in Infants and Children, J. A. M. A. **156**:1321-1323 (Dec. 4) 1954.

314. Lasagna, L.: A Comparison of Hypnotic Agents, J. Pharmacol. & Exper. Therap. **111**:9-20 (May) 1954.

315. Schlegel, H. E., Jr., and Swan, K. C.: Ocular Penetration of Procaine Following Subconjunctival Injection, A. M. A. Arch. Ophth. **52**:774-778 (Nov.) 1954.

316. Scheie, H. G.; Ellis, R. A.; Eckenhoff, J. E., and Spencer, R. W.: Long-Lasting Local Anesthetic Agents in Ophthalmic Surgery, A. M. A. Arch. Ophth. **53**:177-190 (Feb.) 1955.

317. Kohn, J.; Rutter, A. G., and Vitali, M.: Prolonged Local Analgesia with Benzocaine-Urethane Solution, Brit. M. J. **2**:682-684 (Sept. 18) 1954.

318. Schlegel, H. E., Jr., and Swan, K. C.: Benoxinate (Dorsacaine) for Rapid Corneal Anesthesia, A. M. A. Arch. Ophth. **51**:663-670 (May) 1954.

319. Bettini, L., and Gallia, L.: L'Ipotonia bulbare da iniezione retrobulbare di novocaina-adrenalina, Boll. ocul. **33**:771-780 (Nov.) 1954.

320. Feldberg, W.: On Some Physiological Aspects of Histamine, J. Pharm. & Pharmacol. **6**:281-301 (May) 1954.

321. d'Ermo, F.: Antistaminici e occhio, Boll. ocul. **33**:449-462 (Aug.) 1954.

322. Finkelstein, M.; Spencer, W. A., and Ridgeway, E. R.: Chlorpromazine and Tissue Metabolism, Proc. Soc. Exper. Biol. & Med. **87**:343-344 (Nov.) 1954.

323. Friend, D. G., and Cummins, J. F.: Use of Chlorpromazine in the Treatment of Nausea and Vomiting of Uremia, New England J. Med. **250**: 997-999 (June 10) 1954.

324. Marks, J. H.: Use of Chlorpromazine in Radiation Sickness and Nausea from Other Causes, New England J. Med. **250**:999-1001 (June 10) 1954.

325. Chinn, H. I., and Sheldon, G. L.: Effect of Chlorpromazine on Emesis After Radiation, Proc. Soc. Exper. Biol. & Med. **86**:293-295 (June) 1954.

326. Homburger, F., and Smithy, G.: Chlorpromazine in Patients with Nausea and Vomiting Due to Advanced Cancer, New England J. Med. **251**: 820-822 (Nov. 11) 1954.

327. Handford, S. W.; Cone, T. E., Jr.; Chinn, H. I., and Smith, P. K.: Drugs Preventing Motion Sickness at Sea, J. Pharmacol. & Exper. Therap. **111**:447-453 (Aug.) 1954.

328. Friedgood, C. E., and Ripstein, C. B.: Chlorpromazine (Thorazine) in the Treatment of Intractable Hiccups, J. A. M. A. **157**:309-310 (Jan. 22) 1955.

329. Sadove, M. S.; Levin, M. J.; Rose, R. F.; Schwarz, L., and Witt, F. W.: Chlorpromazine and Narcotics in the Management of Pain of Malignant Lesions, J. A. M. A. **155**:626-628 (June 12) 1954.

330. Hershenson, B. B.; Isaac, S. J.; Romney, S. L., and Reid, D. E.: A New Sedative (Antipsychomotor) Drug Useful in Labor: Preliminary Report, New England J. Med. **251**:216-219 (Aug. 5) 1954.

331. Bower, W. H.: Chlorpromazine in Psychiatric Illness, New England J. Med. **251**:689-692 (Oct. 21) 1954.

332. Elkes, J., and Elkes, C.: Effect of Chlorpromazine on the Behavior of Chronically Overactive Psychotic Patients, Brit. M. J. **2**:560-565 (Sept. 4) 1954.

333. Garmany, G.; May, A. R., and Folkson, A.: Use and Action of Chlorpromazine in Psychoneuroses, Brit. M. J. **2**:439-441 (Aug. 21) 1954.

334. Lancaster, N. P., and Jones, D. H.: Chlorpromazine and Insulin in Psychiatry, Brit. M. J. **2**:565-567 (Sept. 4) 1954.

335. Bierent, M. P.: La Chlorpromazine (45.60 R. P.) en ophtalmologie, Bull. Soc. opht. France, pp. 408-414, June, 1954.

336. Rea, E. L.; Shea, J., and Fazekas, J. F.: Hypotensive Action of Chlorpromazine, J. A. M. A. **156**:1249-1250 (Nov. 27) 1954.

337. Stevenson, T. D., and Sjoerdsma, A.: Blood Pressure in Patients with Hypertension Following Intramuscular Chlorpromazine, Proc. Soc. Exper. Biol. & Med. **86**:726-728 (Aug.-Sept.) 1954.

338. Boardman, R. H.: Fatal Case of Toxic Hepatitis Implicating Chlorpromazine, Brit. M. J. **2**:579 (Sept. 4) 1954.

339. Zatuchni, J., and Miller, G.: Jaundice During Chlorpromazine Therapy, New England J. Med. **251**:1003-1006 (Dec. 16) 1954.

340. Van Ommen, R. A., and Brown, C. H.: Obstructive-Type Jaundice Due to Chlorpromazine (Thorazine): Report of 3 Cases, J. A. M. A. **157**: 321-325 (Jan. 22) 1955.

341. Vaughan, D. G., Jr.: Xerophthalmia, A. M. A. Arch. Ophth. **51**:789-798 (June) 1954.

342. Hart, P. L. de V.: Carcinoma Complicated by Proximal Motor Neuropathy Due to Vitamin-B Deficiency, Brit. M. J. **1**:606-609 (March 13) 1954.

343. Bean, W. B., and Hodges, R. E.: Pantothenic Acid Deficiency Induced in Human Subjects, Proc. Soc. Exper. Biol. & Med. **86**:693-698 (Aug.-Sept.) 1954.

344. Morris, G. E.: Use of Vitamin C in Acne Vulgaris, A. M. A. Arch. Dermat. & Syph. **70**: 363-364 (Sept.) 1954.

345. Welsh, A. L.: Lupus Erythematosus: Treatment by Combined Use of Massive Amounts of Pantothenic Acid and Vitamin E, A. M. A. Arch. Dermat. & Syph. **70**:181-198 (Aug.) 1954.

346. Agarwal, L. P., and Adhaulia, H. N.: Role of Vitamin A in the Healing of Corneal Ulcers, Ophthalmologica **128**:6-14 (July) 1954; Am. J. Ophth. **38**:810-816 (Dec.) 1954.

347. Agarwal, L. P., and Datt, K.: Role of Nicotinic Acid in Healing of Corneal Ulcers, Am. J. Ophth. **37**:764-767 (May) 1954.

348. Ferguson, T. M.; Atkinson, R. L., and Couch, J. R.: Relationship of Vitamin E to Embryonic Development of Avian Eye, Proc. Soc. Exper. Biol. & Med. **86**:868-871 (Aug.-Sept.) 1954.

349. De Hoff, J. B., and Ozazewski, J.: Alpha Tocopherol to Treat Diabetic Retinopathy, Am. J. Ophth. **37**:581-582 (April) 1954.

350. Halsted, J. A.; Gasster, M., and Drenick, E. J.: Absorption of Radioactive Vitamin B_{12} After Total Gastrectomy, New England J. Med. **251**: 161-168 (July 29) 1954.

351. Meulengracht, E.: Treatment of Pernicious Anaemia with Very Small Quantities of Pyloric Mucosa and Vitamin B_{12}, Brit. M. J. **1**:838-841 (April 10) 1954.

352. Jerzy Glass, G. B.; Boyd, L. J., and Stephanson, L.: Intestinal Absorption of Vitamin B_{12} in Humans As Studied by Isotope Technic, Proc. Soc. Exper. Biol. & Med. **86**:522-526 (July) 1954.

353. Swendseid, M. E.; Gasster, M., and Halsted, J. A.: Limits of Absorption of Orally Administered Vitamin B_{12}: Effect of Intrinsic Factor Sources, Proc. Soc. Exper. Biol. & Med. **86**:834-836 (Aug.-Sept.) 1954.

354. Becker, B.; Allen, R.; Winter, F. C.; Maengwyn-Davies, G., and Friedenwald, J. S.: Role of the Adrenal Cortex and Vitamin B_{12} in Diabetic Retinopathy, Am. J. Ophth. **38**:53-59 (July, Pt. II) 1954.

355. Chow, B. F.; Rosen, D. A., and Lang, C. A.: Vitamin B_{12} Serum Levels and Diabetic Retinopathy, Proc. Soc. Exper. Biol. & Med. **87**:38-39 (Oct.) 1954.

356. Folk, M. R.: Lipoliqund in Treatment of Hemorrhagic Diabetic Retinopathy, A. M. A. Arch. Ophth. **53**:93 (Jan.) 1955.

357. Bellavia, M., and Pellegrino, F.: Retinite pigmentosa sperimentale e vit. B_{12}, Gior. ital. oftal. **7**:169-175 (March-April) 1954.

358. Gifford, E. S., Jr., and Maguire, E. F.: Band Keratopathy in Vitamin D Intoxication: Report of a Case, A. M. A. Arch. Ophth. **52**:106-107 (July) 1954.

359. Planten, J. T., and Hoppenbrouwers, R.: Experiments on Intra-Ocular Hyaluronidase Administration, Ophthalmologica **127**:117-121 (Feb.) 1954.

360. Alfano, J. E., and Clampit, J.: Injection of Hyaluronidase into the Anterior Chamber of the Rabbit Eye, Am. J. Ophth. **39**:198-202 (Feb.) 1955.

361. Smillie, J. W.: Effect of Streptokinase on Simulated Hyphema, with a Study of Its Toxicity to Anterior Chambers of Rabbits, Am. J. Ophth. **37**:911-917 (June) 1954.

362. O'Rourke, J. F.: An Evaluation of Intraocular Streptokinase, Am. J. Ophth. **39**:119-136 (Feb., Pt. II) 1955.

363. Portfolio, A. G.: Streptokinase-Streptodornase (Varidase) in Treatment of Corneal Ulcers, A. M. A. Arch. Ophth. **52**:557-563 (Oct.) 1954.

364. Taylor, A.; Overman, R. S., and Wright, I. S.: Studies with Crystallin Trypsin: Results and Hazards of Intravenous Administration and Its Postulated Role in Blood Coagulation, J. A. M. A. **155**:347-351 (May 22) 1954.

365. Pereira, R. F.; Aicaguer, O., and Galvan, C.: La Tripsina en el tratamiento de las trombosis venosas retinianas, Arch. oftal. Buenos Aires **29**: 431-434 (Aug.) 1954.

366. Innerfield, I.: Trypsin Given Intramuscularly in Chronic, Recurrent Thrombophlebitis, J. A. M. A. **156**:1056-1058 (Nov. 13) 1954.

367. Martin, G. J.; Brendel, R., and Beiler, J. M.: Inhibition of Egg-White Edema by Proteolytic Enzymes, Proc. Soc. Exper. Biol. & Med. **86**:636-638 (Aug.-Sept.) 1954.

368. Kleinfeld, G., and Havif, D. V.: Effect of Trypsin and Chymotrypsin on the Granuloma Pouch, Proc. Soc. Exper. Biol. & Med. **87**:585-586 (Dec.) 1954.

369. Selye, H.: Effect upon Inflammation of Topical Treatment with Trypsin, Proc. Soc. Exper. Biol. & Med. **86**:6-8 (May) 1954.

370. Bettman, J. W., and Fellows, V.: A Scintillation Counter for the Diagnosis of Intraocular Melanomas, Am. J. Ophth. **39**:170-177 (Feb., Pt. II) 1955.

371. Becker, J., and Scheer, K. E.: Die Bedeutung der radioaktiven Isotope fur die Augenheilkunde, von Graefes Arch. Ophth. **155**:227-237 (March) 1954.

372. Eisenberg, I. J.; Leopold, I. H., and Sklaroff, D.: Use of Radioactive Phosphorus in Detection of Intraocular Neoplasms, A. M. A. Arch. Ophth. **51**:633-641 (May) 1954.

373. Eisenberg, I. J.; Terner, I. S., and Leopold, I. H.: Use of P^{32} as an Aid in Diagnosis of Intraocular Neoplasms; Further Observations, A. M. A. Arch. Ophth. **52**:741-750 (Nov.) 1954.

374. Thomas, C. I.; Krohmer, J. S.; Storaasli, J. P., and Friedell, H. L.: Detection of Intraocular Tumors by the Use of Radioactive Phosphorus, Am. J. Ophth. **38**:93-99 (July, Pt. II) 1954.

375. Snodgrass, M. B.; Lenihan, J. M., and Primrose, D. A.: Radioactive Phosphorus as an Aid to the Diagnosis of Malignant Melanoma of the Eye, Brit. J. Ophth. **38**:553-559 (Sept.) 1954.

376. Kirkland, R. H.: Impaired Organic Binding of Radioiodine by the Thyroid Following Radioiodine Treatment of Hyperthyroidism, J. Clin. Endocrinol. **14**:565-571 (May) 1954.

377. Blumgart, H. L.; Freedberg, A. S., and Kurland, G. S.: Treatment of Incapacitated Euthyroid Cardiac Patients with Radioactive Iodine, J. A. M. A. **157**:1-4 (Jan. 1) 1955.

378. Verel, D.: Treatment of Polycythæmia Rubra Vera with Radioactive Phosphorus, Proc. Roy. Soc. Med. **47**:857-859 (Oct.) 1954.

379. Kent, E. M.; Moses, C.; Ford, W. B.; Kutz, E. R., and George, R. S.: Radioactive Isotopes in Management of Carcinomatosis of Serous Body Cavities, A. M. A. Arch. Int. Med. **94**:334-340 (Sept.) 1954.

380. Emery, E. W.: Three Years' Use of a Cobalt^{60} Unit, Proc. Roy. Soc. Med. **47**:853-857 (Oct.) 1954.

381. Kaae, S.: Carcinoma at the Corneal Limbus Treated with Strontium^{90} Applicator, Acta ophth. **32**:69-75, 1954.

382. Michaelson, I. C.; Gluecker, L., and Stieglitz, E.: Influence of Low-Voltage X-Radiation on Inhibition and Prevention of New Vessels in Cornea: Comparison with Influence of Cortisone, A. M. A. Arch. Ophth. **52**:77-84 (July) 1954.

383. Haik, G. M.; Lyda, W.; Waugh, R. L., Jr., and Ellis, G.: Cataract Formation Following Beta-Ray Radium Therapy; Report of 4 Cases, Am. J. Ophth. **38**:465-470 (Oct.) 1954.

384. McDonald, J. E.; Hughes, W. F., Jr., and Peiffer, V. G.: Beta Radiation Cataracts, A. M. A. Arch. Ophth. **53**:248-259 (Feb.) 1955.

385. Puntenney, I., and Shoch, D.: The Ciliary Body in Radiation Cataract, Am. J. Ophth. **38**:673-682 (Nov.) 1954.

386. Kulwin, M. H., and Buley, H. M.: Radiobiologic Mechanisms in the Skin, A. M. A. Arch. Dermat. & Syph. **70**:417-425 (Oct.) 1954.

387. Rambach, W. A.; Alt, H. L., and Cooper, J. A.: Protective Effect of Hypoxia Against Irradiation Injury of the Rat Bone Marrow and Spleen, Proc. Soc. Exper. Biol. & Med. **86**:159-161 (May) 1954.

388. Gerschman, R.; Gilbert, D. L.; Nye, S. W., and Fenn, W. O.: Influence of X-Irradiation on Oxygen Poisoning in Mice, Proc. Soc. Exper. Biol. & Med. **86**:27-29 (May) 1954.

389. Byrnes, V. A.; Brown, D. V.; Rose, H. W., and Cibis, P. A.: Retinal Burns—New Hazard of the Atomic Bomb, J. A. M. A. **157**:21-22 (Jan. 1) 1955.

390. Byrnes, V. A.; Brown, D. V.; Rose, H. W., and Cibis, P. A.: Chorioretinal Burns Produced by Atomic Flash, A. M. A. Arch. Ophth. **53**:351-364 (March) 1955.

391. Beattie, J. W., and Howells, L. H.: Biological Actions and Therapeutic Applications of Nitrogen Mustard, Quart. J. Med. **23**:231-254 (April) 1954.

392. Hutchens, J. O., and Podolsky, B.: Effect of Nitrogen Mustards on Cell Division in Chilomonas Paramecium and Saccharomyces Cerevisiae, J. Cell. & Comp. Physiol. **43**:205-228 (April) 1954.

393. Miller, Z.: Effect of Methyl-Bis (Beta Chloroethyl) Amine on Aerobic Glycolysis of Thymus Lymphocytes, Proc. Soc. Exper. Biol. & Med. **87**:170-171 (Oct.) 1954.

394. Podolsky, B., and Hutchens, J. O.: Some Effects of Nitrogen Mustards on Metabolism of Chilomonas Paramecium and Saccharomyces Cerevisiae, J. Cell. & Comp. Physiol. **43**:229-245 (April) 1954.

395. Ricketts, C. R.: The Blood Anticoagulant Effect of Short Chain-Length Dextran Sulphates, Brit. J. Pharmacol. **9**:224-228 (June) 1954.

396. Cass, R.; Head, K. W.; Riley, J. F.; Stroud, S. W., and West, G. B.: Heparin and Histamine in Mast Cell Tumours, J. Physiol. **125**:47P (July) 1954.

397. Herzstein, J.; Wang, C. I., and Adlersberg, D.: Effect of Heparin on Plasma Lipid Partition in Man: Studies in Normal Persons and in Patients with Coronary Atherosclerosis, Nephrosis and Primary Hyperlipemia, Ann. Int. Med. **40**: 290-306 (Feb.) 1954.

398. Fasoli, A.; Glassman, M. D.; Magid, E. B., and Foa, P. P.: Serum Lipoproteins in Experimental Diabetes: II. Action of Heparin in Vivo on Lipoproteins of Depancreatized Dogs, Proc. Soc. Exper. Biol. & Med. **86**:298-301 (June) 1954.

399. Grossman, M. I.; Palm, L.; Becker, G. H., and Moeller, H. C.: Effect of Lipemia and Heparin on Free Fatty Acid Content of Rat Plasma, Proc. Soc. Exper. Biol. & Med. **87**:312-315 (Nov.) 1954.

400. Rothfeld, B.; Williams, C. H.; Thaler, W. J., and Rodas, J. M.: Effect of Dicumarol on Localized Shwartzman Reaction, Proc. Soc. Exper. Biol. & Med. **87**:5-7 (Oct.) 1954.

401. Rall, D. P.; Smith, N. H., and Kelly, M. G.: Effect of Anticoagulants on Local Shwartzman Reaction, Proc. Soc. Exper. Biol. & Med. **88**: 241-243 (Feb.) 1955.

402. Rosenman, R. H.; Solomon, B.; Byers, S., and Friedman, M.: Arresting Effect of Heparin upon Experimental Nephrosis in Rats, Proc. Soc. Exper. Biol. & Med. **86**:599-603 (July) 1954.

403. Clatanoff, D. V.; Triggs, P. O., and Meyer, O. O.: Clinical Experience with Coumarin Anticoagulants Warfarin and Warfarin Sodium, A. M. A. Arch. Int. Med. **94**:213-220 (Aug.) 1954.

404. Kruesi, O. R., and Schilling, F. J.: Clinical Evaluation of Phenylindandione as an Anticoagulant, New England J. Med. **251**:927-931 (Dec. 2) 1954.

405. Chalmers, J. N.; Dixon, M. F., and Polack, W.: Antagonistic Effect of Oral Vitamin K_1 on the Action of Ethyl Biscoumacetate and Phenylindanedione, Brit. M. J. **2**:956-959 (Oct. 23) 1954.

406. Makous, N., and Vander Veer, J. B.: Severe Drug Sensitivity Reaction to Pheninidione (Phenylindandione), J. A. M. A. **155**:739-741 (June 19) 1954.

407. Jewell, P.; Pilkington, T., and Robinson, B.: Heparin and Ethyl Biscoumacetate in Prevention of Experimental Venous Thrombosis, Brit. M. J. **1**:1013-1016 (May 1) 1954.

408. Evans, W.: Anticoagulant Therapy in Coronary Occlusion, Proc. Roy. Soc. Med. **47**:318-323 (May) 1954.

409. Gilchrist, A. R., and Tulloch, J. A.: Anticoagulants in Coronary Disease, Brit. M. J. **2**: 720-724 (Sept. 25) 1954.

410. Wright, I. S., and McDevitt, E.: Cerebral Vascular Diseases: Their Significance, Diagnosis and Present Treatment, Including the Selective Use of Anticoagulant Substances, Ann. Int. Med. **41**:682-698 (Oct.) 1954.

411. Appelmans, M., and Lamotte, R.: La Coagulation sanguine dans les thromboses des veines rétiniennes, Ophthalmologica **129**:1-22 (Jan.) 1955.

412. Leo, L. S., and Lidman, B.: Dicumarol in Retinitis Pigmentosa, Resulting Changes in Visual Acuity and Visual Fields: A Preliminary Report, Am. J. Ophth. **39**:46-51 (Jan.) 1955.

413. Cuendet, J. F., and Michels, V.: Le Film de fibrine dans le traitement des kératites, Ophthalmologica **127**:301-304 (April-May) 1954.

414. Weisser, C. W.: Fibrin Film Treatment of Corneal Diseases, A. M. A. Arch. Ophth. **51**:681-686 (May) 1954.

415. Shafrir, E.; de Vries, A., and Katchalski, E.: Action of Poly-α-Amino Acids on Clotting of Fibrinogen by Thrombin, Proc. Soc. Exper. Biol. & Med. **87**:63-67 (Oct.) 1954.

416. Morrison, W. H.: Stability of Aqueous Solutions Commonly Employed in the Treatment of Primary Glaucoma: III. Experimental Procedure and Findings; Summary and Conclusions, Am. J. Ophth. **37**:744-757 (May) 1954.

417. Vaughn, D. G., Jr.: The Contamination of Fluorescein Solutions, Am. J. Ophth. **39**:55-61 (Jan.) 1955.

418. Murphy, J. T.; Allen, H. F., and Mangiaracine, A. B.: Preparation, Sterilization, and Preservation of Ophthalmic Solutions, A. M. A. Arch. Ophth. **53**:63-78 (Jan.) 1955.

419. Klein, M.; Millwood, E. G., and Walther, W. W.: On the Maintenance of Sterility in Eye-Drops, J. Pharm. & Pharmacol. **6**:725-732 (Oct.) 1954.

420. Stenbeck, A., and Östholm, I.: Ointments for Ophthalmic Use, Acta ophth. **32**:405-423 (April) 1954.

421. Askovitz, S. I.: An Improved Electrolysis-Iontophoresis Unit, Am. J. Ophth. **38**:719-720 (Nov.) 1954.

422. Erlanger, G.: Iontophoresis, a Scientific and Practical Tool in Ophthalmology, Ophthalmologica **128**:232-246 (Oct.) 1954.

423. Gilger, A. P., and Potts, A. M.: Studies on the Visual Toxicity of Methanol: V. Role of Acidosis in Experimental Methanol Poisoning, Am. J. Ophth. **39**:63-86 (Feb., Pt. II) 1955.

424. Potts, A. M.: Visual Toxicity of Methanol: VI. Clinical Aspects of Experimental Methanol Poisoning Treated with Base, Am. J. Ophth. **39**: 86-92 (Feb.) 1955.

425. Praglin, J.; Spurney, R., and Potts, A. M.: An Experimental Study of Electroretinography: I. The Electroretinogram in Experimental Animals Under the Influence of Methanol and Its Oxidation Products, Am. J. Ophth. **39**:52-62 (Feb., Pt. II) 1955.

426. Vainio-Mattila, B., and Zewi, M.: Quinine Amblyopia and the Electro-Retinogram (ERG), Acta ophth. **32**:451-461 (April) 1954.

427. Turtz, C. A.: Visual Toxic Symptoms from Digitalis, Am. J. Ophth. **38**:400-401 (Sept.) 1954.

428. Goodside, V.: Ocular Findings in Hypercalcemia: A Clinical and Histologic Study, Am. J. Ophth. **38**:856-858 (Dec.) 1954.

429. Breinin, G. M., and DeVoe, A. G.: Chelation of Calcium with Edathamil Calcium-Disodium in Band Keratopathy and Corneal Calcium Affections, A. M. A. Arch. Ophth. **52**:846-851 (Dec.) 1954.

430. Oksala, A.: Äthylendiamintetraessigsäure in der Behandlung von Verletzungen des Auges durch Kalk, Klin. Monatsbl. Augenh. **125**:99-102, 1954.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

John M. McLean, M.D., Presiding

Joseph Laval, M.D., Secretary

Feb. 4, 1955

Report on 200 Partially Blind Patients Examined for Correction of Subnormal Vision. DR. GERALD FONDA.

Two hundred patients were examined for corrective lenses for subnormal vision at the Lighthouse (New York Association for the Blind). Lenses were prescribed for 101 patients; all of them were later interviewed in order to decide whether the lenses were beneficial to them. The examiner concluded that 60 patients were rehabilitated to an acceptable degree.

All these patients suffering from subnormal vision had been treated by ophthalmologists, many of whom had not had their vision corrected by available means.

The types of ocular pathology chiefly responsible for the subnormal vision in the cases in which lenses were prescribed were as follows:

TABLE I.—*Pathologic Conditions Producing Subnormal Vision*

Pathologic Conditions	No. of Cases
Optic atrophy	18
Corneal opacities	14
Glaucoma	13
Postoperative aphakia for congenital cataract	12
Albinism	9
Macular degeneration	6
Myopic degeneration	6
Retinitis pigmentosa	5
Chorioretinitis	4
Cataract	4
Diabetic retinopathy	2
Keratoconus	2
Miscellaneous	6
Total	101

The lenses prescribed were classified as regular, simple magnifying, doublet magnifying, and contact. The vision of 24 patients was improved by regular lens correction; e. g., an albino who was wearing no glasses was greatly benefited by the following correction: O.D.: -8.50 sph $\bigcirc$ $+1.00$ cyl, ax 90; O.S.: -11.00 sph $\bigcirc$ $+1.75$ cyl, ax 90. There were a few aphakic patients examined who had been wearing no correction; consequently, they appreciated the usual strong plus correction.

Fifty-four patients were given prescriptions for simple magnifying lenses. These corrections ranged from $+8.00$ sph to $+30.00$ sph. Many of the strong plus corrections were given in the form of bifocals.

Doublet magnifiers were prescribed for 19 patients. The powers ranged from $\times 8$ to $\times 20$ magnification.

Contact lenses were fitted to five patients.

No telescopic lenses were prescribed in this series of cases. The fact that no telescopic spectacles were prescribed may be startling to the reader, as it was to the examiner. A greater demand for telescopic lenses had been anticipated, owing to the prevalence of television. The majority of patients with subnormal vision enjoyed television and could look at it for hours by sitting at distances of from 1 to 3 ft. from the screen. Those who possessed telescopic lenses preferred to sit closer to the screen and not wear the lenses. There were no patients in this group

who the examiner believed would benefit more from telescopic lenses than from a simple magnifying lens for near vision. However, one patient, a shoemaker, was wearing telescopic lenses at his work. In such a case no other magnifying device would supplant the telescopic lenses, because a maximum working distance is essential for this trade.

Table 3 records the degree of visual defect encountered in this project, as well as the number in each group and the incidence of successful cases. The Table shows that 65% of the patients having subnormal vision seeking correction have a visual acuity of 20/200 or less. Sixty-six per cent of this group had successful correction. The two patients whose vision ranged between 20/40 and 20/20 suffered from advanced chronic simple glaucoma with markedly constricted visual fields.

SUMMARY AND CONCLUSIONS

Of 200 patients with subnormal vision, the examiner believed that 101 could be sufficiently rehabilitated with subnormal vision lenses.

Of the 101 patients for whom lenses were prescribed, 60 were considered by the patient and the examiner to have successful correction.

TABLE 2—*Types of Lenses Prescribed*

Type of Lenses	No. Prescribed	No. Successful
Regular	24	10 (42%)
Simple magnification	52	31 (58%)
Doublet magnifiers	19	14 (74%)
Contact	5	3 (60%)
Telescopic	0	.....

TABLE 3—*Degree of Visual Defect, Incidence, and Percentage of Patients with Successful Correction*

Range of Visual Acuity	No.	No. (%) with Successful Correction
1/200	1	.....
3/200-10/200	40	28 (70%)
11/200-20/200	28	17 (61%)
20/180-20/100	22	13 (59%)
20/80-20/50	7	1 (14%)
20/40-20/20	2	.....
Illiterate	1	.....

Relative frequencies of ocular pathology responsible for subnormal vision are enumerated.

The types of lenses prescribed, the number of each kind, and the percentage of successful results are tabulated.

The degree of visual defect, the incidence, and percentage of cases with successful correction are tabulated.

Patients suffering from subnormal vision are ophthalmologists' patients who have not had correction by available means.

Most cases of subnormal vision can be given correction by a careful refraction or by the use of strong plus lenses.

There seems to be a small need for telescopic spectacles, especially for distant use.

Doublet magnifiers are successful in many cases in which no other type of lens is satisfactory.

Contact lenses are most useful in some cases of corneal pathology.

Principles of Magnification in Subnormal Vision Problems. DR. DAN M. GORDON and MR. CHARLES RITTER.

The application of our knowledge of the principles of magnification can result in rehabilitating a high percentage of cases of low vision.

Types of low-vision aids which can be utilized are (1) high plus lenses, up to as much as +20 to +40 D.; (2) hand magnifiers, with or without built-in illumination, and with or without stands; (3) projection devices, such as the American Foundation's Megascope or the Franklin Institute's device; (4) contact glasses; (5) microscopic lenses of Feinbloom or Bechtold; (6) telescopic lenses, or (7) a combination of (1) and (2).

The opthalmologist has traditionally been prejudiced in favor of lenses that can be worn on the nose, and traditionally has been accustomed to stop at an add of approximately +3.00 D. The use of much higher additions with the reading material held closer to the face will render it possible for many near-blind patients to read. Many forms of magnifiers are available and beneficial.

Most of the devices are for near vision only. Telescopic lenses, of which many new models are available, are useful for distant function.

DISCUSSION OF PAPERS BY DR. FONDA AND DR. GORDON AND MR. RITTER

DR. ALFRED KESTENBAUM: The presentations of Dr. Fonda and Dr. Gordon attract the attention to the burning problem of reading devices for patients with poor vision. But in looking for the required device, one should rely not on the method of trial and error, but on calculation. In 1952 I reported a simple formula for this calculation, based on the concept of the reciprocal of vision. If a person has vision of 20/200, or 1.10, the reciprocal of vision is 10. If a person has vision of finger counting at 10 ft., whereas a normal person is able to count fingers at 200 ft., the reciprocal of vision is 20.

Since Jaeger type 5, which corresponds, more or less, with usual typewritten letters, can be read at 1 meter by a normal eye, an eye with a reciprocal of vision of n (vision—20/20 n) could read Jaeger type 5 in 1/n-meter distance. In order to focus a letter in 1/n-meter distance, the eye needs a glass of +n D. (an available accommodation has to be subtracted).

This calculation, therefore, results in a simple formula: A patient is able to read usual typewritten letters if he uses a convex glass of just as many diopters as the reciprocal his vision amounts to. If the reciprocal of his vision is 5 or 10 or 20, he is able to read typewritten letters with +5 D. or +10 D. or +20 D., respectively.

This formula has been based on the supposition that the visual acuity found with Snellen's chart, or the "far vision," and the visual acuity found with a reading chart, or the "near vision," are congruent. As a matter of fact, they were found to be congruent, with only four exceptions. In an eye with a central opacity of the cornea or of the lens, the near vision is less than the far vision because of the narrowing of the pupil in near gaze. In a peripheral opacity of the cornea or of the lens, the near vision is better than the far vision. In an eye with irregular astigmatism the near vision is better than the far vision. Finally, in a case of partial macular lesion, where only parts of the macula are preserved, near vision appears to be less than far vision, because in the reading of a reading chart one not only has to see single letters, as on Snellen's chart, but has to compose the letters to words, so that "holes" in the macular area are more disturbing. With these four exceptions, the near vision and the far vision are congruous, so that the formula here given is valid and an exact calculation of the required device is possible.

We may divide patients with poor vision into three groups:

1. Patients with a vision (after correction) down to 20/50 may read with a reading glass slightly stronger than usual. This old method has been used generally.

2. Patients with vision between 20/60 and 20/200. For them three devices are at our disposition:

(*a*) A strong plus glass as reading glass. It must be calculated according to the foregoing formula: The strength of the plus glass must be equal to the reciprocal of the patient's vision.

(*b*) A magnifying lens, or loupe. Its strength must be found on the basis of the same formula. Usually, loupes are marked not in diopters but according to their

magnification, which conventionally refers to 0.25-meter object distance. The transformation is simple. The magnification of a lens equals one-fourth its power, measured in diopters. A lens of +10 D. gives a × 2½ magnification; a lens of +20 D. gives a × 5 magnification. Therefore, one prescribes a loupe of a magnification which equals one-fourth the patient's reciprocal of vision.

(*c*) A telescopic system, which is also marked in figures of magnification. Again, the patient needs a magnification equaling one-fourth his reciprocal of vision.

Which of these three devices—or modifications—is prescribed depends on the individual occupation or need of the patient. Strong reading glasses require a relatively close distance of the letters; a magnifying loupe allows a larger distance, but one hand of the patient is occupied holding the loupe, etc.

3. For patients with still lower vision, between 20/300 (reciprocal of vision=50), only one device is at our disposal. A telescopic lens is not available, since the strongest telescopic lens gives only × 2.2 magnification. A magnifying loupe of such a strength (+15 to +60 D., or × 4 to × 12 magnification) is not available for reading, because the visual field enclosed by the margin of the lens becomes so narrow that only a few letters, or not even an entire letter, is visualized at once. Therefore, for these patients we have to prescribe a strongly magnifying reading glass, calculated according to the above formula. A patient with an absolute central scotoma and vision of finger counting at 5 ft. (reciprocal of vision=1/40) is enabled by a reading glass of +40 D. to read usual typewritten letters (of course, at the close distance of 2.5 cm.).

Since usual reading glasses of such a strength would give a severe peripheral aberration, I described in 1942 microglasses, glasses with a smaller diameter, so that the peripheral aberration is decreased, e. g., for +40 D., a diameter of 12 mm.

Such "microglasses" may be made by grinding or by glueing a plane-convex lens upon a plane glass or by the use of a so-called linen tester in a spectacle.

Another form of strong glasses with decreased peripheral aberration is given in Feinbloom's glasses.

In conclusion, it is to be emphasized that the required glass has to be calculated and that the method of trial and error is to be abandoned. Down to visual acuity of 20/50 one uses a stronger reading glass; between 20/60 and 20/200 there is a choice of a strong reading glass, a loupe, and a telescopic system; the choice has to consider the patient's occupation. Below 20/200 only a magnifying eyeglass is at our disposal.

The calculation of the strong reading glass is made with the formula: The required number of diopters equals the reciprocal of the patient's vision. The calculation of the loupe and of the telescopic system is made with the formula: The required magnification equals one-fourth the reciprocal of the patient's vision.

DR. JOSEPH I. PASCAL: Dr. Fonda and Dr. Gordon have covered the subject so well that there is hardly anything to add. It is interesting to note that Dr. Fonda stressed the fact that in a very large percentage of the subnormal vision cases the simple application of a strong plus add of, say, 10 or 15 D. is all that is necessary. Dr. Gordon, in addition, showed the many marvelous devices, magnifiers of one type or another, now available, and some in the process of being perfected, which are very effective in improving vision where a simple strong reading add is not adequate. The papers thus complement each other.

There is one point which I believe has not been stressed enough, namely, that the seeing process of the subnormal-vision patient differs in some respects from the visual process in the normal-sighted. Persons with subnormal vision do not depend so much upon clear retinal images, something we are accustomed to think of in connection with clear vision. They learn to see more by what we would designate as clues. To use a far-fetched illustration: Perhaps one could recognize Jimmy Durante by his nose. This process of learning to see by clues explains many phenomena in subnormal vision work, such as Dr. Gordon's case in which there was a central macular scotoma. Part of the image is missing, but there are enough clues from the parts that register on the functioning retina to make things recognizable.

One other point I want to call to the attention of both speakers. I have had it in mind for a long time, that is, the need for an institute for visual rehabilitation in a large city like New York and in other large centers. Such an institute need not be a wholly charitable institution or a wholly commercial institution, but somewhat akin to our privately endowed hospitals. With the increasing life expectancy, there will be thousands and thousands of partially sighted persons needing visual rehabilitation so that they may become useful members of society. Such an institute not only would meet these needs but would serve as a center for research and for teaching physicians interested in engaging in such work in their private practice.

DR. GERALD FONDA: In reply to Dr. Pascal: There is considerable collaboration going on at present with different persons throughout the country who are interested in this work, and at this very moment we are trying to organize some kind of research that will bring in many people who are interested in the problem from many points of view. We are trying to get those who are interested to agree on some place in which to start.

DR. DAN M. GORDON: It is interesting that Mr. Ritter, my co-author, is with the American Foundation for the Blind, Dr. Fonda is from the New York Association for the Blind, and I am with the National Council to Combat Blindness. We have representatives of these three organizations and others working together in a common cause. The American Foundation for the Blind is organizing a series of projects on this subject. At Cornell, in the Eye Department, the work will be integrated with the Department of Rehabilitation, where I believe it should properly be put. This carries out Dr. Pascal's excellent suggestion.

"The Long Cane." DR. RICHARD E. HOOVER, Baltimore.

"The Long Cane" is the title of a documentary film which tells the story of a phase of a patient's blindness. It illustrates two things: what a hospital can do to help the newly blinded, and a way of teaching blind people common skills, especially how to get about without sight.

A veteran whose eyesight was damaged in the war subsequently loses all useful sight. He is depicted in the process of treatment, from a time of discouragement and regression through gradual steps of learning. He goes through a period of half-conscious awareness of his own fear of blindness, realization of fear, and action to overcome it. Hospital personnel, including a blinded veteran, give encouragement to independence, which is in contrast to a public attitude that at times shows hostility toward challenges brought to the patient, although these challenges are carefully planned.

It is significant that this is a hospital program, designed to give eye patients who lose their sight a practical initiation to the problem of not being able to see. Although the environment and methods shown here have been developed in a Veterans Administration Hospital for blinded veterans and service men, some of the psychology could be carried over to civilian groups.

For all civilian blind patients the film suggests the advantages of an additional therapeutic process to prepare newly blinded patients for what is coming for them when they stop being patients with eye trouble and become blind people. The Blind Center of the Physical Medicine and Rehabilitation Service of the Veterans Administration Hospital, at Hines, Ill., which is shown in the film, attempts to deal early and logically with the isolation of blind people from the standpoint of common efficiencies. One of the fundamental disadvantages of the blind person in any society is that in the designing and testing of most tools, utensils, and articles, sightlessness is seldom considered. The environment shown in "The Long Cane" represents an effort to make up for the disadavantage of this type of isolation by a pooling of common efficiencies of blindness and by their early introduction under the authority and guidance of medicine before the blind patient has fallen into haphazard habits with regard to his blindness. The long cane from which the film takes its title is symbolic, inasmuch as it is a modified version of a very ancient and common instrument, for which a special and efficient use has been developed for blind people.

This therapeutic endeavor, which can be justified by efficiency, may also be justified because it demonstrates the blind person's ability to admit the hard reality of his situation without panic. This, as much as physical skill, is demonstrated to be the lesson which the patient is learning. Several important methods and principles are shown in the film. One of these is the importance of the equipoise of an exemplary blind person who occupies a position of authority in the therapeutic process. Another factor is the importance of individual assistance. A third is the importance of contact with seeing persons who put their capabilities at the disposal of blind persons while keeping the feelings of sympathy under control, using their sight to find the way things are done without sight, and to show these ways to the blind.

The black and white 16-mm. film is procurable on loan from all Veterans Administration Regional Offices or from Central Office, Vermont and H Sts., Washington 25, D. C. It is in two parts, with a running time of 63 minutes.

DISCUSSION

DR. JOSEPH I. PASCAL: Are there any such facilities available for nonveterans?

DR. RICHARD E. HOOVER: Yes, some of the agencies run by cities and states are now employing orientators; the Catholic Guild in Boston is very active, and many schools are sponsoring programs of this kind. This is just one phase of the problem, but an important one.

Truman L. Boyes, M.D., *Chairman*

Joseph Laval, Secretary

Regular Meeting, May 16, 1955

The Kirby Technique of Intracapsular Cataract Surgery. DR. WALTER J. MAHER.

For the best results in cataract surgery Dr. Daniel Kirby felt that a systematic plan was most helpful for the surgeon.

Preoperative Period.—As soon as the diagnosis of cataract is made, a general check-up is necessary to rule out any systemic disease. Dr. Kirby found it helpful in the weeks prior to operation to eliminate all stimulants and to give small doses of phenobarbital.

The patient is admitted to the hospital the afternoon prior to operation and is immediately given phenobarbital ½ grain (0.032 gm.) t. i. d. Pentobarbital (Nembutal) sodium, 1½ grains (0.11 gm.) is given at bedtime. Two hours prior to operation pentobarbital sodium 1½ grains is given, followed in one-half hour by chloral hydrate, 20 grains (1.2 gm.) per rectum. One hour before operation Meperidine (Demerol) hydrochloride, 50 mg. is given intramuscularly. If possible, it is wise to check the reaction to the pentobarbital before giving the chloral hydrate. In many old or asthenic patients the latter medication is a little too much, and they will be too heavily sedated. The patient is then brought to the operating room and should be quiet and relaxed, but awake.

Akinesia.—Curare is given intravenously by an anesthetist according to the Kirby-Flagg technique. It is supplemented by a modified Van Lint and a subconjunctival injection of Cobefrin. No retrobulbar injection is given. Concerning the retrobulbar method, Dr. Kirby said:

> I am not worried about the obvious retrobulbar hemorrhage in which the operation has to be postponed, but rather in the many cases in which there is a slow oozing but no frank hemorrhage. This ooze increases the volume of the orbit and necessarily causes pressure on the globe and a bulging forward of the vitreous following delivery of the lens.

In our hands, curare has consistently given excellent relaxation and, contrary to the opinion of many, is safe.

The Operation.—A very shallow fornix-based flap is made with a Bard-Parker #15 blade. Then, with fixation upon the medial rectus, a knife section is made and is enlarged with scissors. Corneoscleral 6-0 chromic nonabsorbable surgical sutures are inserted at approximately 10 and 2 o'clock, with another through the

cornea at 12 o'clock. The latter suture is to be used for elevation of the flap during the delivery. All three sutures have knots approximately 5 mm. from the end. Next, with the assistant elevating the flap, two large peripheral iridotomies are made at 10 and 12 o'clock. The anterior chamber is irrigated thoroughly with saline to remove all clots and any loose pigment from the iris. The lens is tilted at 6 o'clock with the muscle hook; the flap is elevated, and the lens capsule is grasped as near the superior equator as possible. The lens is lifted out of the patellar fossa and, by means of what Dr. Kirby referred to as inverse tumbling, the zonule is separated and the lens removed. In about 10% of the cases it is necessary to strip the zonule directly. The sutures are then tied and the 12 o'clock suture passed through the scleral edge and tied. If necessary, one or two additional corneoscleral sutures may be used. Then the conjunctiva is sutured at 3 and 9 o'clock, and, if necessary, air is injected into the anterior chamber.

Electromyography of the Extraocular Muscles. Dr. G. M. Breinen and Dr. Joseph Moldaver.

This paper will be published in a future issue of the Archives.

DISCUSSION

Dr. Joseph Moldaver: In any of the peripheral neuropathies it is very easy to stimulate nerves and the corresponding muscles and therefore make a diagnosis of lower motor neuron lesion. It is very simple to demonstrate whether the paralysis is due to complete denervation or partial denervation or is the result of a block of conduction. A typical example of the latter is Bell's palsy, in which the prognosis of the lesion can be ascertained by the stimulation of the nerve and the various muscles that the facial nerve supplies.

The third, fourth, and sixth nerves cannot be stimulated in patients, at least in normal clinical conditions; but we can now record the action potential of the different extraocular muscles with needle electrodes. We can then demonstrate in some cases of paralysis of the third, fourth, or sixth nerve whether or not there is fibrillation, which characterizes denervation. The existence of potentials with volition and fibrillations in the same muscle would determine the diagnosis of a partial lesion. The absence of fibrillation with complete paralysis might be suggestive of a block of conduction, such as is seen usually in the pressure type of paralysis.

Two slides will demonstrate complete denervation in a patient who had a third nerve paralysis, resulting from an aneurysm. (Slide) These fibrillation potentials are spontaneous, and they are not activated by volition. They are not accompanied by any motor unit discharge, and they do not disappear when the antagonist muscle contracts. The second slide shows more detail of the fibrillation potentials. They were recorded with a faster speed of the camera.

With the recording of action potentials, we shall be able to study not only lesions affecting the different nerves, but also cases of muscular dystrophy, and eventually myasthenia gravis as well.

Further Consideration for the Surgical Correction of Congenital Epicanthus, So-Called Blepharophimosis. Dr. Edmund B. Spaeth, Philadelphia.

This paper is to be published in the *American Journal of Ophthalmology*.

DISCUSSION

Dr. Wendell L. Hughes: The discussion of this condition is one that most of us enter into with a great deal of timidity, because of the difficulty of obtaining a satisfactory result. One is sometimes limited by bony deformities, in which the orbit is small and widely separated, and in the amount of soft tissue readjustment that can be made by the bony deformity underlying it. Dr. Spaeth has outlined some interesting historical facts in relation to this condition, and we are greatly indebted to him for bringing us up to date in that respect.

We have all seen cases of this defect in families, in some of which some siblings have been affected and others have not been affected. I have at present under my care a young girl whose one sister is affected and whose other two siblings are not affected. The father is a doctor, and he was affected. I know of one other family in which 11 siblings are affected. I am sorry I could not locate the slide of this rather striking family group, ranging from one small member up to the father, who was practically a giant, with this interesting condition. The family is Negro, and probably some of the other men around New York have seen it. It was from the Bronx. When a man comes from Philadelphia to talk to us, we have to bring up something bigger and better from New York; so that is the Bronx's contribution.

I have been working on this problem for some time and have attacked it with the idea of correcting three particular deformities: One is the wide intercanthal distance between the medial canthi; the second in these cases of blepharophimosis tarsalis, in which we have a very small interpalpebral fissure, is the encroachment of the lateral canthus over the eye, for which a simple canthotomy temporally suffices, and then, of course, there is the ptosis. The ptosis can be taken care of in many ways; in most cases there is enough power in the levator to warrant an Eversbusch procedure, which has been my favorite for correcting the ptosis. I have not had to use any other procedure in these cases. The problem of the distance between the medial canthi, however, is the crux of the situation, in my opinion, and one which is handled in so many different ways that one hesitates to suggest his own favorite one. The one that I have used is that of moving the medial canthus medially, thus lessening the distance between the medial canthi, like the procedure which Dr. Spaeth illustrated in the early part of his lecture, the horizontal Y-V procedure. (Slides illustrating the operative method were shown.)

I enjoyed Dr. Spaeth's discussion very much, and I certainly have benefited by his masterful handling of this difficult subject.

DR. EDMUND B. SPAETH, Philadelphia: I am pleased that Dr. Hughes also feels that the importance of the correction of these cases rests with the rearrangement of tissues. But I want to say that this technique of mine, which I have presented to you, was essentially for epicanthus inversus. The case that Dr. Hughes showed us so beautifully is the results of epicanthus palpebralis, and I have never seen a more satisfactory result. I wish some of my epicanthus palpebralis cases would be as good as his after the operation; I wish also that some of the cases that the plastic surgeons do looked half as good. I want to call attention again to the difficulties connected with the correction of epicanthus inversus.

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Edmund B. Spaeth, M.D., *Chairman*

William E. Krewson, 3rd, M.D., *Clerk*

April 21, 1955

Elephantiasis Nostras: Report of a Case. DR. ARTHUR BOBB JR. (read by DR. HANHAUSEN, by invitation).

The case of a 59-year-old man with bilateral painless swelling of the lids of 11 years' duration was presented. Examination revealed bilateral nontender, diffuse, nonpitting edema of the upper and lower lids, which resulted in protrusion of the latter by 2 cm. from the orbital margin. There were no other significant findings on physical or laboratory examination. Surgical removal of the excess tissue in the lower lids was done. Microscopic examination of the excised tissue revealed diffuse infiltration of the subcutaneous tissue and orbicularis with chronic inflammatory cells; extensive fibromatosis, and increased number of blood vessels and lymphatics. A diagnosis of elephantiasis nostras was made. The clinical and pathologic features of this disease were discussed.

This case is believed to be only the second recorded in the American ophthalmologic literature.

DISCUSSION

DR. GLEN GIBSON: The justification for this presentation is, first, the rarity of the condition and, second, the remarkable relief afforded by a relatively simple surgical procedure for this patient's inability to read, due to the fact that the redundant skin completely covered his bifocal segments.

The problem of differential diagnosis may be difficult at times, due to the numerous local, intracranial, and systemic etiologic factors which may be responsible for somewhat similar clinical conditions. Examples of the various types of conditions which warrant differential diagnosis may be illustrated by slides.

Slide 1 is a photograph of a patient that illustrates unilateral lid enlargement caused by a local chronic and recurrent inflammatory condition in the lids or orbit, which may be due to any of a large variety of different organisms. This case was one of lymphedema due to a circumscribed abscess in the lid. The edema was nontender and remained for many months after the original inflammatory process had subsided, probably due to enlargement of the lymphatics, as described by the author.

Slide 2 illustrates a diffuse neoplastic condition which may arise from tumors of the blood vessels, lymphatics, or nerves. This particular one is an elephantiasis of the lid due to hemangioma, the specimen of which is shown in the inset.

Slide 3 shows a type of chronic lymphedema which is due to a nondiffuse type of neoplastic disease, a primary carcinoma of the antrum. This photograph was taken one year after removal of the eye, the floor of the orbit, and the major part of the antrum. It may be noted that the edema ends abruptly at the margin of the orbit, where the fascia is attached to the perioseum at the margin of the orbit. This condition is nontender, and the tumor has been removed; yet this highly edematous process persists.

Slide 4 shows lymphedema of the eyelids which is due to an intracranial process. This patient's difficulty is the result of a traumatic carotid-cavernous fistula which followed a gunshot wound of the orbit.

Slide 5 is an extreme example of a lymphedema of the upper and lower eyelids due to an intracranial cause. This patient has a large meningioma which is intracranial and involves the frontal lobe. It extends through the optic foramen and has produced a large bony defect. It is most probable that this is complicated by the presence of a carotid-cavernous fistula, because there is marked pulsation of the markedly distended lids. This patient has been seen by numerous neurosurgeons, and the consensus is that the condition is inoperable.

Slide 6 is an extreme case of lymphedema of the eyelids with a systemic cause. This patient was found to have an advanced degree of myxedema.

Slide 7 shows bilateral symmetrical enlargement of the upper lids due to blepharochalasis. In the initial stage of this disease there are episodes of swelling of the eyelids, characterized by smooth, soft, shiny skin. In the latter, atrophic stages the skin becomes thin and baggy and hangs down, much as it did in the present case of elephantiasis nostras. Blepharochalasis is usually differentiated from elephantiasis nostras by the fact that this condition usually involves the upper lid, whereas elephantiasis usually involves the lower lids. There are examples, however, in which the reverse may be the case. Blepharochalasis usually affects young persons and is characterized by marked atrophic changes in the skin in the terminal stage. It may at times present a problem in differential diagnosis.

These illustrative photographs demonstrate that elephantiasis of the lids presents a complex problem which warrants a complete survey from the point of view both of the local condition and of the systemic state, as well as roentgenologic study, in order to find, whenever possible, the exact cause of the condition.

DR. JOSEPH V. KLAUDER: I was under the impression that this condition was originally described by one who needs no introduction to ophthalmologists, Jonathan Hutchinson. He described the condition just before the turn of the last century and labeled it solid edema of the face.

Since its original description, there has been considerable amplification of our knowledge of elephantiasis nostras. As you know, its clinical concept comprises

an inflammatory and a noninflammatory phase. This was well illustrated in the lantern slides presented by Dr. Gibson.

In differential diagnosis one should consider the pathologic process called the Melkersson-Rosenthal syndrome. Comparable to elephantiasis nostras, this syndrome is characterized by recurring localized swelling with or without fever, eventually terminating in permanent swelling. The usual site of the swelling is the upper lip, but any area of the face may be involved. This swelling comprises one manifestation, the initial one, of the syndrome; the other symptoms are an enlarged, plicated tongue and, finally, facial paralysis. The two last symptoms, of course, do not ensue in elephantiasis nostras. Only in the early stage of the Melkersson-Rosenthal syndrome is there clinical resemblance to elphantiasis nostras.

Mention may be made of a comprehensive review of this syndrome (Touraine, R. L.: Le Syndrome de Melkersson-Rosenthal, *Ann. Dermat. et Syph.* **81:** 409–414, 1954). The disease is apparently uncommon in America. Most of the reported cases have appeared in German and Swiss literature.

I first became acquainted with the disease when visiting German clinics a few years ago, where I saw several patients who had the disease. The histopathologic picture of the localized swelling is tuberculoid and is unlike that of elephantiasis nostras. The opinion has been expressed that the disease is an expression of sarcoidosis. The evidence of this, however, is not very convincing.

Pituitary Apoplexy: Relief of Ambylopia by Prompt Surgical Intervention. Dr. Henry A. Shenkin.

Two cases of acute hemorrage into a pituitary adenoma with resulting amblyopia were reported. In addition, the hemorrage in one patient caused an acute hypothalamic and Addisonism crisis. Prompt surgical intervention (within eight hours in one patient and in three days in the other) permitted complete recovery of vision in one patient and recovery of useful vision in the other. Surgical decompression did relieve one patient of a severe endocrine crisis and hypothalamic dysfunction by removing pressure from remaining normal pituitary tissue and the hypothalamus.

Tonography: Technical Difficulties and Control Studies. Dr. Robert W. Spencer (by invitation), Dr. Ernest D. Helmick (by invitation), and Dr. Harold G. Scheie.

This paper will appear in a future issue of the Archives.

DISCUSSION

Dr. Cyril M. Luce: I congratulate Dr. Scheie and his group on the excellent work that they have done with tonographic studies. At Wills Eye Hospital we also have had a few problems with our tonometer, some of them similar to the ones that these men have encountered. We use a Leeds & Northrup recording instrument. I think that in general the Sanborn is probably the easier one to handle. We found, first, that the zero point of the recorder did not coincide with the zero on the tonometer scale, and we had quite a drift in the zero point. We had a number of consultations with the engineers, who felt that the zero drift was due to a change in voltage output as the tubes of the tonometer became heated. It was necessary, therefore, for us to take daily calibrations with the recorder and to readjust each day the zero point with that on the tonometer. We purchased a new electric tonometer and found that it gave us an entirely new set of zero points, and again we had to restandardize the machine. We used resistors similar to the ones used on the Sanborn type. Dr. Askovitz kindly helped us to assemble a constant-voltage transformer. Our current at Wills apparently is not as stable as that at the University. It was necessary for us to have a movable lamp for fixation. We still have one problem that we have not solved—that is how to secure fixation in a one-eyed person. We have had some difficulty with these subjects.

At present we have obtained tonograms on about 350 patients, a number of which have had repeat studies, and we have been interested partly in how tonograms

correlate with the results of other diagnostic procedures for glaucoma, including water-provocative tests and mydriasis tests; we have also been interested in tonograms taken prior to surgery and those taken after operation. The 57 patients who have had these studies fall into one of the following groups: patients with tonograms and water-provocative tests, 24%; patients with mydriasis tests, 35%; those with tonograms prior to surgery, 39%, and patients with tonograms after surgery, only 2%. Of the 13 who have had both water-provocative tests and tonograms, only 1 had positive results in both. Two had a negative water-provocative test and a positive tonogram. One had a negative water-provocative test and tonogram. In the doubtful range of 0.11 to 0.15, we found a positive water-provocative test and a negative tonogram on two occasions. Of the 19 patients who had mydriasis tests, 4 had positive tonograms and mydriasis tests. Of 22 who had tonograms prior to surgery, all but 4 had greatly impaired outflow; and of those who had tonograms after surgery, 2 had reached the normal outflow and 2 of them had continued impaired flow. At present at Wills we consider tonography most useful on a clinical basis in the diagnostic survey of glaucoma suspects, and it has been of great use to us in the evaluation of cases for proper surgical procedure, especially as to whether filtering or nonfiltering procedures should be done. In postsurgical cases, it has been useful in evaluating the failure or success of the surgery, especially in trephine operations or cyclodialysis, the results of which can be correlated with the tonogram through gonioscopy.

Dr. E. Howard Bedrossian: I congratulate Dr. Spencer on the very important and useful information he has given us. He has presented two important facts: 1. There may be a large variation (as much as 25%) in tonographic readings taken at the same time of day, but on different occasions, in normal subjects. 2. A recording device is not essential for accuracy, since the data obtained are just as reliable by taking initial and final readings as when a recording device is used.

I too feel there is a definite variation in individual readings. Therefore, before I draw any conclusions, I take an average of at least three morning readings and an average of at least three evening readings on the same patient. In this way the normal variation in readings taken at the same time of day may be reduced to a minimum. In the patients that I reported at the last annual Wills Eye conference, I had taken the average morning and average evening readings and then compared the rate of formation of aqueous with the rate of outflow of aqueous. The findings in chronic simple glaucoma showed a definite phasic variation in the coefficient of outflow. The facility of outflow was diminished in the morning readings as compared with that of the evening readings.

If one takes tonographic readings every 4 hours for a period of only 24 to 36 hours, the individual variations in the normal may be so much that one obtains insignificant or erroneous phasic variations. However, if one takes an average number of readings, say at least three or four readings, for the morning and then three or four readings for the evening, one may then be able to show some significant changes during the different times of the day in the coefficients of outflow.

Dr. Spencer's findings have convinced me that one aqueous outflow study alone is not enough on which to make a definite diagnosis, especially in borderline cases, and therefore it is extremely important that aqueous outflow studies be repeated at least two or three times, on different occasions, before a definite diagnosis is made on the basis of this test alone.

Dr. Francis Heed Adler: The work presented this evening is certainly a labor of love, but not "love's labor lost." History repeats itself, and every time we have a new method developed in the laboratory and applied clinically, we find reports in the literature which are premature because inadequate control tests have been done. You will recall that a few years ago certain instruments were devised to measure dark adaptation which were applied clinically before adequate controls were run. The literature was flooded with reports of school children supposed to have subclinical vitamin A deficiency on the basis of these dark adaptation determinations. Because of these studies, it was claimed in many other

clinical conditions the patients were suffering from vitamin A deficiency. All these reports eventually turned out to be erroneous, simply because the method had not been adequately tested, and, as a result chiefly of the work of Hecht and Schlaer, the necessary controls were worked out.

The type of work presented this evening represents a back-breaking job, which in a way is a great sacrifice; but it is work which lays the sure foundation for future knowledge, and for that reason I feel the authors deserve our thanks and congratulations. We now have in the literature adequate controls for tonography; and as we read subsequent reports, we shall be in a far better position to say whether or not the data presented are or are not significant.

DR. HAROLD G. SCHEIE: We have discussed some of the difficulties encountered by us in beginning tonography. As you have learned from Dr. Spencer's presentation, some of them were overcome only after considerable delay. The most annoying of our troubles was lack of standardization of tonometers. Each of the tonometers used by us had to have the voltage output altered considerably, such that it fell within the range which could be registered on a Sanborn recorder. We were aided by Dr. Morton Grant and the Sanborn Company in overcoming this difficulty. Fortunately, the electric current in our laboratory was sufficiently stable that fluctuations in voltage supplying the tonometer were of no consequence.

Once our appartus was working well, it seemed necessary to do control studies on normal eyes—first, to check our own technique and then to reinforce similar control studies in the literature. It seemed unwise to proceed with the method in glaucomatous patients until the method in our hands seemed of accuracy equal to that of other workers. As reported by Dr. Spencer, you have learned that the lower limits of aqueous outflow was 0.15 cu. mm/min/mm. Hg, a figure compatible with that of other workers. There is a definite plus or minus error in tracings repeated on the same eye of approximately 0.045 cu. mm/min/mm. Hg, which means that any tracing of, for example, 0.16/min/mm. Hg, could be interpreted as either 0.205 or 0.105, the one being a fairly normal value and the other definitely abnormal. It is impossible, therefore, to make an arbitrary interpretation of a single tracing. Although electrotonography is of some diagnostic value, it should not be considered as supplanting other, more easily obtained, clinical findings. We believe that this is true when the method is used in following the patient with simple chronic glaucoma; if, for example, the patient's field remains unchanged and his tension is well controlled, operation should not be done regardless of the facility of aqueous outflow.

Dr. Grant has made a brilliant contribution to our understanding of the mechanics and classification of glaucoma, but we feel that many observations will have to be made to determine its exact status in the clinical management of glaucoma other than as a diagnostic aid.

Obituaries

CLYDE A. CLAPP, M.D.
1880-1955

Clyde Alvin Clapp was born in Chatham, Ohio, May 29, 1880, the son of Alvin Rice and Martha Talbot Clapp. He died in Baltimore April 9, 1955, after a lingering illness of several months, following an exploratory operation for carcinoma of the stomach.

He was educated in the public schools of Ohio and received his medical degree in 1902 from the Baltimore Medical College. After a short period of general practice in Baltimore, he became associated with the late Dr. Frank Crouch, and formed a partnership which lasted for 25 years. As his main interest was ophthalmology, he soon confined his work entirely to that field. He was Associate Professor of Ophthalmology at the Baltimore Medical College from 1910 to 1913; Associate and later

CLYDE A. CLAPP, M.D.
1880-1955

Associate Professor of Ophthalmology at the University of Maryland from 1913 to 1932, and Professor and later Professor Emeritus of Ophthalmology at the university of Maryland from 1932 to 1955. He was also Associate Professor of Ophthalmology at the Johns Hopkins University and Visiting Ophthalmologist to the Johns Hopkins Hospital from 1923 to 1948 and Associate Professor Emeritus from 1948 to 1955. He was surgeon at the Baltimore Eye and Ear Hospital from 1919 till the time of his death and served in many capacities in the administration of that hospital, from 1947 until his death being chairman of the staff.

In 1922, Dr. Clapp was elected to membership in the American Ophthalmological Society. He was a member of the American Medical Association, the American College of Surgeons, the American Academy of Ophthalmology and Otolaryngology, and the Ophthalmological Society of the United Kingdom. He was a member of the Baltimore City Medical Society and the Maryland Chirurgical Faculty.

His first investigative work was done while still a medical student, and from then on he was a frequent contributor to the medical literature. In 1919 he made the first of his almost yearly trips to the medical clinics of England, Scotland, and the continent of Europe. In 1934 he published a book, "Cataract, Its Etiology and Treatment."

Dr. Clapp married Lillian A. Dickson in 1905. They had two children, Roger Alvin and Clyde Melville, both of whom survive. Mrs. Clapp died in 1914. In 1928 he married Ellen L. Richardson.

His main hobby was travel, and with Mrs. Clapp his annual holidays were usually spent visiting places of interest in many parts of the world. This gave wide opportunity for the exercise of his second hobby, photography. This resulted in a husband-and-wife team of colored movie and travelogue entertainment of almost professional level, enjoyed by many groups, including various medical societies.

Dr. Clapp's interest in organized medicine was life long and genuine. Not only did he support activities in his own specialty on a local and national scale, but he also was interested in the problems and policies of the whole profession, and was a regular attendant at the general meetings. It may justly be said that he was an ornament to medicine. Further than that, he was a loyal friend, a good citizen, and a highly principled, conscientious physician. His passing means a great loss to the profession and the whole community.

ANGUS L. MACLEAN, M.D.

STEPHEN POLYAK, M.D.

1889-1955

Stephen Polyak was found dead on the morning of March 9, 1955. Fate decreed that he, the outstanding authority on the anatomy and pathology of the visual system, should be the victim of disease processes that in the course of years gradually and almost entirely destroyed his extramacular vision. It is remarkable with what energy he resisted the encroachments of disease. Even the day before his death he devoted to work on his last book. The writing of this book, a comprehensive volume on the vertebrate visual system, was indeed a heroic accomplishment, achieved in a period of ill health during the last ten years. It is true that it could not have been achieved without the never-failing support of his wife, Donna, and, it should be added, not without the help of the University of Chicago, which supported his work and made it possible for him to continue his investigations.

The story of his scientific life can be succinctly told by giving the complete titles of the three books which he wrote in the course of his career and which embody the results of his scientific endeavors: 1. The Main Afferent Fiber Systems of the Cerebral Cortex in Primates: An Investigation of the Central Portions of the Somato-Sensory, Auditory, and Visual Paths of the Cerebral Cortex, with Consideration of Their Normal and Pathological Function, Based on Experiments with Monkeys (pp. XIV + 370, with 96 illustrations; Berkeley, Calif., University of California Press, 1932). 2. The Retina: The Anatomy and the Histology of the Retina in Man, Ape, and Monkey, Including the Consideration of Visual Functions, the History of Physiological Optics, and the Histological Laboratory Technique (pp. X + 721, including 130 pages of bibliography and 100 illustrations; University of Chicago Press, 1941). 3. The Vertebrate Visual System: Its Origin, Structure, and Function and Its Manifestations in Disease with an Analysis of Its Role in the Life of Animals and in the Origin of Man, preceded by a Historical Review of Investigations of the Eye, and of the Visual Pathways and Centers of the Brain (in press; a royal octavo volume of about 1,600 pages, including 551 illustrations, 27 in color, and a bibliography of about 10,000 references; University of Chicago Press). As he has pointed out in the preface of the last book, this work represents the outcome of "the almost continuous labor of nearly three decades." He himself read the galley proofs of the first 14 chapters, and it is hoped that this monumental volume will be published in the not too distant future.

Born on Dec. 13, 1889, in northern Croatia (Yugoslavia), Stephen Polyak was educated at the Classical Gymnasium in Zagreb and at the University of Graz, Austria. His medical training, which he began in 1909 at the Medical School in Graz, was interrupted in 1914 by the events of World War I. While attached to the Medical Corps of the Austro-Hungarian army, he participated in the battles at the Russian front during the first three months of the war, but then was captured by the Russians and interned at Kiev. Subsequently he was employed as a physician in a Russian military hospital and in the Medical Corps of the Serb Volunteer Divisions. Although the general staff of the Russian army granted his request to return to Serbia and issued a special passport to him, he was unsuccessful in his attempt to reach Serbia. However, he was permitted to register at the

Medical School of the New-Russia University in Odessa, where he received, after studying medicine for two semesters, his M.D. degree in the fall of 1916. It is worth recording that he saw, during a review of the Serb troops in Odessa, the Czar and his family at close range, little realizing, as he wrote later, that they would be murdered in about a year and that he was in fact witnessing "the funeral cortège of the last Romanovs . . . and the last pale glory of Russia's Empire on that warm summer day in the year 1916." The 1917 revolution found him on the medical staff of the Second Serb Volunteer Division, in the divisional field hospital located in a small town of southern Russia not far from the Dnieper River. With other members of the Serb divisions, he was permitted to leave Russia by way of Archangel, on the White Sea. The Russian ship that took him around Norway to Scotland anchored at the entrance of the Cromarty Firth at the beginning of October, 1917. His subsequent journey took him through England and France,

STEPHEN POLYAK, M.D.
1889-1955

where he almost died as the result of an inoculation by a French sanitary soldier, to Salonika, in Greece, where he joined the Serbian army and participated in its battles in Macedonia and Albania until the end of the war. It was only in 1920, after about six years in uniform, that he became a civilian again. In the same year, the University of Zagreb granted him an M.D. degree. While an assistant in the Department of Neurology and Psychiatry in this university, 1920-1928, he became actively engaged in research not only in Zagreb, but also in other centers. A letter of his written in French and addressed to the Instituto Cajal in Madrid brought him, to his surprise, a complete set of the "Trabajos" of the University of Madrid, which he diligently studied during the following years. His researches took him in 1921 to the Neurological Institute at the University of Vienna (Obersteiner's Institute), in 1924-1925 to the University of London (for work with G. Elliot Smith), in 1925 to Madrid (to visit Ramón y Cajal), and in 1926-1927 to Chicago, where he was attracted by the work of C. Judson Herrick and K. S. Lashley. On returning from Chicago to Europe, he found conditions at the University of Zagreb

and in Yugoslavia such that he decided in 1928 to leave his native country and accept an offer from the University of California. He served as Assistant Professor of Neuroanatomy in California until 1930, when he returned to Chicago to spend the remaining 25 years of his life at the University of Chicago. From 1930 to 1937 he was Assistant Professor, and then Associate Professor, of Neurology in the University of Chicago Clinics. From 1937 on he was a member of the Department of Anatomy, in which he held an appointment first as Associate Professor until 1942, and then as Professor of Anatomy from 1942 until his death.

Pavlov's advice, as quoted by Sir William Bragg, was superfluous for Stephen Polyak: "Remember that science demands from a man all his life. If you had two lives that would be not enough for you. Be passionate in your work and your searchings." Stephen Polyak certainly belonged to those scientists who are in the Pavlovian sense "passionate" in their work and their searchings. Ever since the guns turned silent on the European battlefields at the end of the first world war, he had worked almost uninterruptedly and, it may be said, with a burning intensity. His interests extended over a wide domain, from biology and natural history to anthropology and politics, from the history of science to the history of nations, and of Western civilization itself. It is surprising that he found the energy and the time, even during the last months of his life, to put in order and work on a manuscript of about 2000 typewritten pages, a fourth book, a diary dealing with the story of his life and our generation. This book, entitled "Glory to Them All," is another testimony to the universality of his interests. And it is characteristic that it has the subtitle "Recollections of a Nobody." Stephen Polyak's life, unlike that of many other scientists, was not marred by the seeking for fame, power, advancement, and "the glories of this world." No wonder, therefore, that the world did not seek him out to heap special honors upon him as the years sped on. He was so intensely absorbed in his work that he did not even take time to join many societies or attend many scientific meetings, although he consented to serve on the editorial board of the *Journal of Comparative Neurology* from 1937 to 1948. However, the tributes paid to him by leading neuroanatomists and other scientists leave little doubt that his work will stand the test of time longer than will generally be the case with the contributions furnished by modern scientists. His fundamental contributions, it must also be remembered, were made almost singlehandedly. Those who were able to witness his methods of work through the years and his attitude toward scientific pursuits could not help but feel that Balfour's characterization of Darwin was also applicable to Stephen Polyak: "He was not a partizan—he really wanted to find out the truth—an attitude of mind seldom found among men of science." His high standards of scientific integrity, the honesty and meticulous care with which he worked or drew conclusions from his work, his humility in the face of intricate and unsolved problems—these virtues as found in Stephen Polyak do not, it is unfortunately true, readily grow or thrive in the microclimate of present-day scientific institutes or universities. Being entirely devoid of personal ambition, he lived a life in which ultimately nothing mattered except his scientific work, and the problems, demands, and exigencies arising in connection with this work. Those words of Francis Bacon that have subsequently been used to introduce one of the most famous books ever produced in the history of Western thought appear to be the very words written across all of Stephen Polyak's scientific endeavors: *De nobis ipsis silemus.*

Heinrich Klüver
University of Chicago

News and Comment

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

Annual Meeting of Section on Ophthalmology, A. M. A.—The annual meeting of the Section on Ophthalmology, American Medical Association, was held in the Dennis Hotel, June 7-9, 1955, during the Annual Meeting of the American Medical Association in Atlantic City, N. J.

Guest of honor speakers were J. W. Tudor Thomas, of Cardiff, Wales, who spoke on "Fixation of Corneal Grafts," and James H. Doggart, of London, England, who spoke on "The Impact of Boxing upon the Visual Apparatus."

The following officers of the Section were elected: A. D. Ruedemann, chairman; John B. Hitz, vice-chairman; Harold G. Scheie, secretary, elected in 1953 for three years; William L. Benedict, delegate to House of Delegates, reelected in 1954 for two years, and Harvey Thorpe, alternate delegate, reelected in 1954 for two years.

The Knapp Medal was awarded to David G. Cogan for his paper "Ocular Dysmetria, Flutter-like Oscillations of the Eyes and Opsoclonus," which was presented before the Section in 1953.

The Price Medal in Ophthalmology was awarded to Frank B. Walsh.

The Section voted to award a cash prize of $250 for the best paper presented before the Section each year and $250 for the best exhibit. The award will be announced not later than one month after the closing of the Section meeting and will come from the Knapp Fund.

International Organization Against Trachoma.—An Extraordinary General Assembly of the I. O. A. T. was held in Paris, May 9, 1955, at 28, rue Saint-Dominique, under the chairmanship of Prof. G. B. Bietti, of Parma, Italy.

Sir Stewart Duke-Elder, President of the International Council of Ophthalmology, and Prof. John C. Snyder, of the Harvard University School of Public Health, attended the sessions.

Tributes to M. A. F. MacCallan, Honorary President, who died on March 31, 1955, were read and the Assembly observed a minute of silence in his honor.

Modification of the Statutes necessitated by the death of the President-Founder, by the obligations of growing internationalization, by the admission of I. O. A. T. to the World Health Organization, and by the increasing number of countries interested in the Organization's activities were adopted. They included the creation of three vice-presidencies, instead of one, and of the position of treasurer.

The officers composing the new council are as follows:

President: G. B. Bietti, Italy
Vice-presidents: Arnold Sorsby, Great Britain
Phillips Thygeson, United States of America
Roger Nataf, France
Secretary general: Jean Sedán, France
Associate secretary: Yasushi Nakamura, Japan
Treasurer: Georges Farnarier, France

Headquarters of the I. O. A. T. will remain in London: 45, Lincoln's Inn Fields (W. C. 2).

All correspondence should be addressed to the Secretary General, 94, rue Sylvabelle, Marseille, France.

The Assembly accepted as corresponding societies the following:

Società Oftalmologica Italiana

Sociedad Oftalmológica Hispano-Americana

Philippine Ophthalmological Society

Secção de Oftalmologia da Sociedade de Ciencias Medicas (Portugal)

Finnish Ophthalmological Society

New England Ophthalmological Society

The next Assembly will be in Madrid in 1956, during the Second Congress of the Société Latine d'Ophtalmologie.

PERSONAL NEWS

Col. William L. Spaulding's Appointment.—Col. William L. Spaulding, 1390 Tewksbury Place, N.W., Washington, D. C., has been named Chief of the Ophthalmology Service at Walter Reed Army Hospital.

SOCIETY NEWS

The American Ophthalmological Society.—The following officers were recently elected for the current year:

President.....Dr. Alan C. Woods, Baltimore

Vice-president.....Dr. Frederick C. Cordes, San Francisco

Secretary-treasurer.....Dr. Maynard C. Wheeler, New York

Editor.....Dr. Gordon M. Bruce, New York

New York Society for Clinical Ophthalmology.—The newly elected officers of the New York Society for Clinical Ophthalmology for the 1955-1956 season are as follows:

President	Bernard Kronenberg
Vice-president	Max Chamlin
Recording secretary	Jesse M. Levitt
Corresponding secretary	Leon H. Ehrlich
Treasurer	Henry M. Kera
Historian	Robert S. Coles
Committee Chairmen	
Program	Abraham Schlossman
Instruction session	Arthur Linksz
Legislative	Benjamin C. Rosenthal
Membership	Howard Agatston
Industrial	Edward M. Douglas

ANNOUNCEMENTS

Winifred Hathaway Memorial Fund.—At the suggestion of the many friends and associates of Winifred Hathaway, a memorial fund has been established in her name by the National Society for the Prevention of Blindness. The Winifred Hathaway Memorial Fund will be devoted to extending that part of the Society's work which concerns the education and health of partially seeing children. Contributions designated for the Fund may be sent in care of the National Society for the Prevention of Blindness, 1790 Broadway, New York 19.

Mrs. Hathaway joined the National Society in 1916 and for 24 years was its associate director. She initiated its campaign of professional education, working particularly on the promotion of educational facilities for partially seeing children. Shortly before her death, last December, she completed the latest revision of "Education and Health of the Partially Seeing Child," the standard textbook used throughout the world.

CORRECTION

In the article "Successful Corneal Transplants in Four Eyes of Two Patients with Lattice Dystrophy," by Drs. Joseph Laval and Ralph I. Lloyd (June issue, page 884), Figures 9 and 11 (pages 886 and 887) have been interchanged. The legend for Figure 9 should read: "Corneal appearance O.D. (left), 1940, and O.S. (right), 1953, before operation."

Books

Reconstructive Surgery of the Eyelids. Second Edition. By Wendell L. Hughes, M.D. Price, $8.50. Pp. 260, with 268 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1954.

The second edition of this excellent text on plastic surgery of the ocular adnexa has been considerably improved and expanded. The techniques of dressings, particularly the application of satisfactory pressure dressings, is dealt with in a new chapter, and this is sufficiently detailed and illustrated that it serves as a bedside manual. The illustrations are particularly good throughout the book.

While in itself the book is complete as a text on reconstructive surgery of the eyelids, it would be a further improvement if a chapter on reconstruction of the orbit were included in future editions, since many of these procedures naturally follow orbital exenteration.

Clinical Use of Corticotropin, Cortisone and Hydrocortisone in Eye Diseases. By Dan M. Gordon, M.D. Price, not given. Pp. 88, with 21 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1954.

The author of this book was one of the first to use corticotropin (ACTH) in eye diseases after the striking results obtained by Hensch in the treatment of rheumatoid arthritis. The paper by Gordon and J. M. McLean appeared in *The Journal of the American Medical Association* in 1950. In the four years between that paper and the appearance of this small manual, thousands of articles have appeared on the use of various corticosteroids. The rapidity with which the scene is changing suggests that it is dangerous to assay a book on this subject, since by the time it comes off the press opinion may have changed considerably. This book is full of examples in which current thought runs counter to statements it contains. For example, the author states, "As newer and clinically more effective forms of ACTH are making their appearance, the eosinophil count becomes even more important as a guide to dosage." Little differentiation is drawn between treatment of acute and treatment of chronic conditions.

Throughout the book the author's experience is documented with case reports of various diseases in which it is now definitely known that corticotropin therapy is without any benefit whatsoever. While the author does not claim that these patients have been benefited, their inclusion implies this possibility, and it would be of greater value to point out that a majority of investigators now consider the drug useless in these conditions.

The book can be recommended only as having historic interest.

Grenz Ray Therapy: Principles, Methods, Practice. By Gustav Bucky, M.D. and Frank G. Combes, M.D. Price, $8.50. Pp. 204, with 62 illustrations. Springer Publishing Co., Inc., 44 E. 23d St., New York 10, 1954.

The physics and technique of grenz radiation are outlined. The effects of this type of radiation on the cell nucleus and cytoplasm are described, and, finally, the histological changes which take place in the skin after radiation. The last half of the book is concerned with the use of grenz rays in various dermatological condi-

tions. There is a short chapter by Felix Sagher and J. Landau on grenz ray therapy in ophthalmology. It is not apparent that grenz rays have much applicability to ophthalmologic conditions, and the book will therefore have slight appeal to ophthalmologists.

Augenhohlenplastik. By Istvan Csapody. Price, not given. Pp. 102, with 71 illustrations. Akademiai Kiado, Budapest, Hungary, 1954.

This short book describes the author's operation for contracted socket. The first chapter deals with the causes of contraction of the socket, and this is followed by a short history of orbitoplasty. In the author's operation a full-thickness graft is kept in place in the enlarged socket by means of a special instrument. The instrument itself consists of two metal pieces which can be separated a variable distance and the separation maintained by a screw clamp. The operation is described in detail, and 104 cases are documented.

Although written in German, the book should be valuable for all interested orbitoplasty.

Index ophthalmologicus. Fourth Edition. Price, $2.75. Pp. 370. Stenfert Kroese Societatem Editoriam, Netherlands, 1954.

The new "Index ophthalmologicus," published by the International Council of Ophthalmology, contains the names and addresses of ophthalmologists throughout the world. Dr. A. C. Copper is to be congratulated on the tedious job of collecting these names and other data which the book contains, such as the main eye hospitals, ophthalmological societies, and ophthalmological periodicals throughout the world. The only objection which can be raised is that in order to find an individual's address one must know what city he lives in. In locating an ophthalmologist in the United States, if one does not know, for example, that he lives in Scranton, a long and tedious search must be made among all the ophthalmologists in the United States. In spite of this deficiency, the new index will fill a long-felt need.

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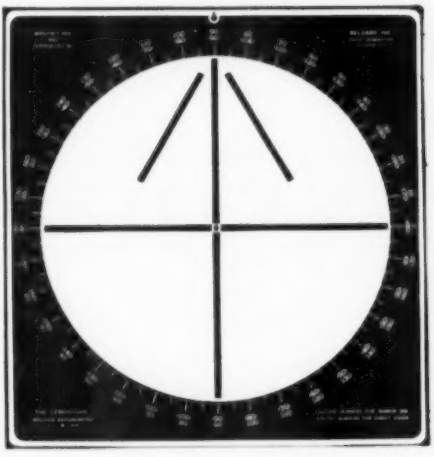

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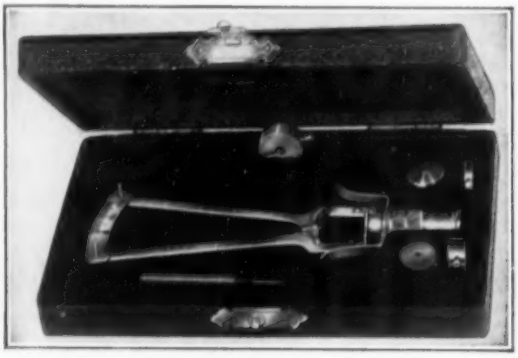

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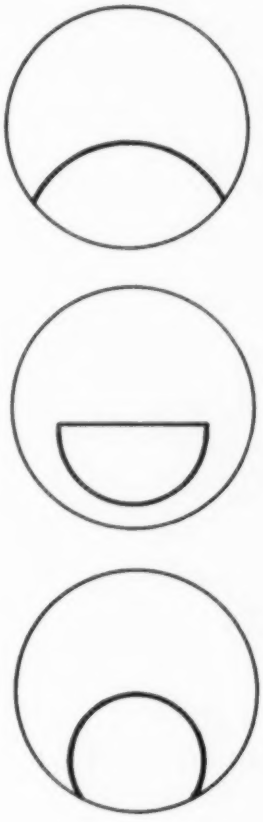

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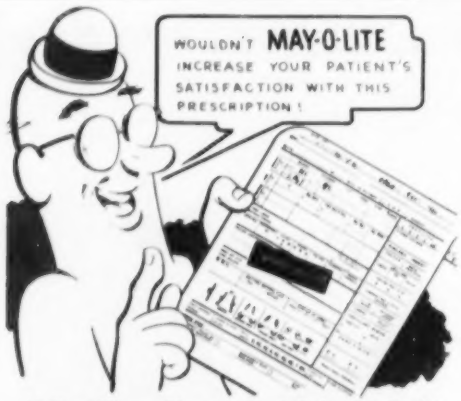

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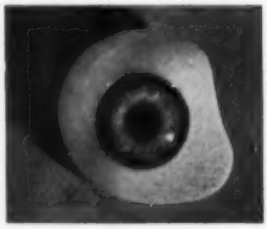

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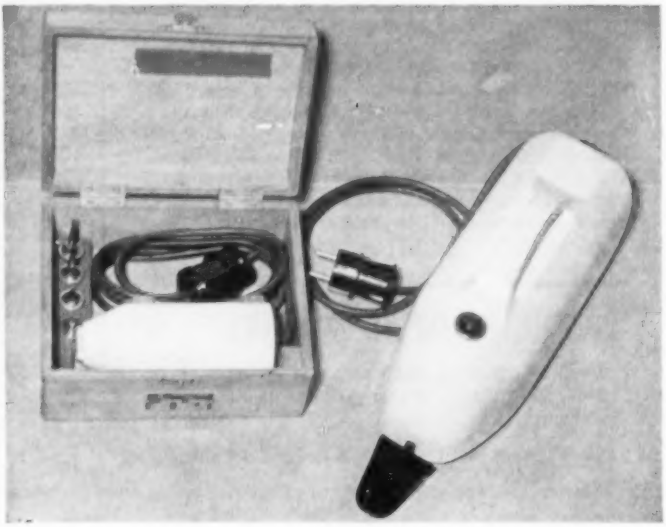

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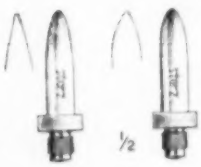

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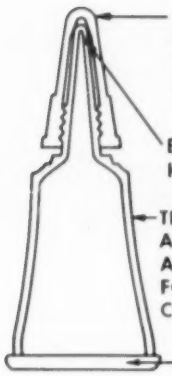
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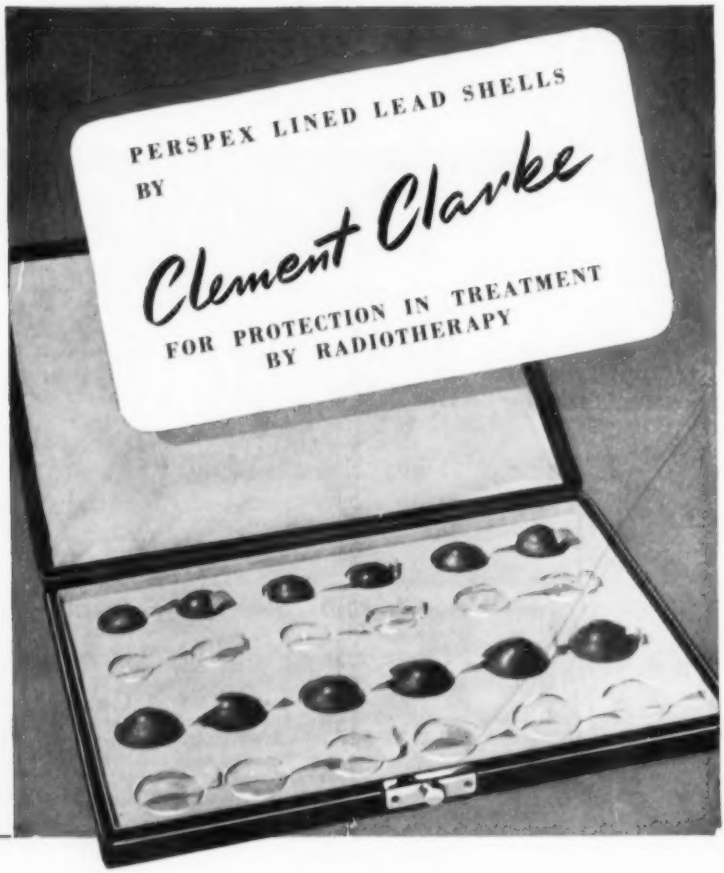

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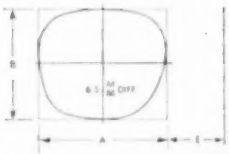

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